(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 February 2007 (08.02.2007)

PCT

(10) International Publication Number
WO 2007/015866 A2

(51) International Patent Classification:
C07D 487/04 (2006.01) *C07D 495/04* (2006.01)
C07D 471/04 (2006.01) *A61P 29/00* (2006.01)
C07D 333/60 (2006.01)

(21) International Application Number:
PCT/US2006/027863

(22) International Filing Date: 18 July 2006 (18.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/701,217	20 July 2005 (20.07.2005)	US
60/701,250	20 July 2005 (20.07.2005)	US
60/701,251	20 July 2005 (20.07.2005)	US
60/701,254	20 July 2005 (20.07.2005)	US
60/701,253	20 July 2005 (20.07.2005)	US
60/701,183	20 July 2005 (20.07.2005)	US
60/780,186	8 March 2006 (08.03.2006)	US
60/790,189	7 April 2006 (07.04.2006)	US

(71) Applicant *(for all designated States except US)*: **KALYPSYS, INC.** [US/US]; 10420 Wateridge Circle, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SEVERANCE, Daniel, L.** [US/US]; 8439 Torrell Way, San Diego, CA 92126 (US). **BORCHARDT, Allen, J.** [US/US]; 5419 Via Carancho, San Diego, CA 92111 (US). **GARDINER, Elisabeth, M., M.** [US/US]; 8438 New Salem Street #81, San Diego, CA 92126 (US). **KAHRAMAN, Mehmet** [TR/US]; 10165 Camino Ruiz #55, San Diego, CA 92126 (US).

(74) Agents: **HO, Raymond, J.** et al.; International Patent Group, Post Office Box 38129, St. Louis, MO 63138 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF P38 KINASE AND METHODS OF TREATING INFLAMMATORY DISORDERS

(57) Abstract: The present invention relates to compounds and methods useful as inhibitors of p38 kinase for the treatment or prevention and treatment of diseases such as inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, angiogenic disorders, infectious diseases, neurodegenerative diseases, and viral diseases.

WO 2007/015866 A2

INHIBITORS OF P38 KINASE AND METHODS OF TREATING INFLAMMATORY DISORDERS

This application claims the benefit of priority of United States provisional applications: No. 60/701,253, filed July 20, 2005; No. 60/790,189, filed April 7, 2006; No. 60/701,254, filed July 20, 2005; No. 60/780,186, filed March 8, 2006; No. 60/701,251, filed July 20, 2005; No. 60/701,250, filed July 20, 2005; No. 60/701,217, filed July 20, 2005; and No. 60/701,183, filed July 20, 2005; all of which are hereby incorporated by reference as if written herein in their entirety.

FIELD OF THE INVENTION

The present invention is directed to novel compounds and compositions and their application as pharmaceuticals for the treatment of disease. Methods of inhibition of p38 kinase activity in a human or animal subject are also provided for the treatment diseases such as inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, angiogenic disorders, infectious diseases, neurodegenerative diseases, and viral diseases.

BACKGROUND OF THE INVENTION

The present invention relates to inhibitors of p38, a mammalian protein kinase involved in cell proliferation, cell death and response to extracellular stimuli. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the present invention and methods of utilizing those compositions in the treatment and prevention of various disorders. The compounds are potent inhibitors of p38 kinase and are useful in the prophylaxis or treatment of p38 kinase mediated diseases or disorders, such as inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, angiogenic disorders, infectious diseases, neurodegenerative diseases, and viral diseases.

Four isoforms of p38 have been described (p38α./β/γ/δ). The human p38α enzyme was initially identified as a target of cytokine-suppressive anti-inflammatory drugs (CSAIDs) and the two isoenzymes found were initially termed CSAID binding protein-1 (CSBP-1) and CSBP-2 [Lee, J. C. et al, Nature (London) 1994, 372, 739-46]. CSBP-2 is now widely referred to as p38α and differs from CSBP-1 in an internal sequence of 25 amino acids as a result of differential splicing of two exons that are conserved in both mouse and human [McDonnell, P. C. et al, Genomics 1995, 29, 301-2]. CSBP-1 and p38α are expressed ubiquitously and there is no difference between the two isoforms with respect to tissue distribution, activation profile, substrate preference or CSAID binding. A second isoform is p38β which has 70% identity with p38α. A second form of p38β, termed p38β2, is also known, and of the two this is believed to be the major form. P38α and p38β2 are expressed in many different tissues. However in monocytes and macrophages p38α is the predominant kinase activity [Lee, J. C., ibid; Jing, Y. et al, J. Biol. Chem. 1996, 271, 10531-34; Hale, K. K. et al, J. Immun. 1999, 162, 4246-52]. P38γ and p38δ (also termed SAP kinase-3 and SAP kinase-4 respectively) have .about.63% and .about.61% homology

to p38α respectively. P38δ is predominantly expressed in skeletal muscle whilst p38δ is found in testes, pancreas, prostate, small intestine and in certain endocrine tissues.

All p38 homologues and splice variants contain a 12 amino acid activation loop that includes a Thr-Gly-Tyr motif. Dual phosphorylation of both Thr-180 and Tyr-182 in the TGY motif by a dual specificity upstream kinase is essential for the activation of p38 and results in a >1000-fold increase in specific activity of these enzymes [Doza, Y. N. et al FEBS Lett., 1995, 364, 7095-8012]. This dual phosphorylation is effected by MKK6 and under certain conditions the related enzyme MKK3 (see FIG. 1) [Enslen, H. et al J. Biol. Chem., 1998, 273,1741-48]. MKK3 and MKK6 belong to a family of enzymes termed MAPKK (mitogen activating protein kinase kinase) which are in turn activated by MAPKKK (mitogen activating protein kinase kinase kinase) otherwise known as MAP3K.

Several MAP3Ks have been identified that are activated by a wide variety of stimuli including environmental stress, inflammatory cytokines and other factors. MEKK4/MTK1 (MAP or ERK kinase kinase/MAP three kinase-1), ASK1 (apoptosis stimulated kinase) and TAK1 (TGF-β-activated kinase) are some of the enzymes identified as upstream activators of for MAPKKs. MEKK4/MTK1 is thought to be activated by several GADD-45-like genes that are induced in response to environmental stimuli and which eventually lead to p38 activation [Takekawa, M. and Saito, H. Cell, 1998, 95, 521-30]. TAK1 has been shown to activate MKK6 in response to transforming growth factor-β (TGF-β). TNF-stimulated activation of p38 is believed to be mediated by the recruitment of TRAF2 [TNF receptor associated factor] and the Fas adaptor protein, Daxx, which results in the activation of ASK1 and subsequently p38.

Several substrates of p38 have been identified including other kinases [e.g. MAPK activated protein kinase 2/3/5 (MAPKAP 2/3/5), p38 regulated/activated protein kinase (PRAK), MAP kinase-interacting kinase 1/2 (MNK1/2), mitogen- and stress-activated protein kinase 1 (MSK1/RLPK) and ribosomal S6 kinase-B (RSK-B)], transcription factors [e.g. activating transcription factor 2/6 (ATF2/6), monocyte-enhancer factor-2A/C (MEF2A/C), C/EBP homologous protein (CHOP), Elk1 and Sap-1a1] and others substrates [e.g. cPLA2, p47phox].

MAPKAP K2 is activated by p38 in response to environmental stress. Mice engineered to lack MAPKAP K2 do not produce TNF in response to lipopolysaccharide (LPS). Production of several other cytokines such as IL-1, IL-6, IFN-g and IL-10 is also partially inhibited [Kotlyarov, A. et al Nature Cell Biol. 1999, 1, 94-7]. Further, MAPKAP K2 from embryonic stem cells from p38α null mice was not activated in response to stress and these cells did not produce IL-6 in response to IL-1 [Allen, M. et al, J. Exp. Med. 2000, 191, 859-69]. These results indicate that MAPKAP K2 is not only essential for TNF and IL-1 production but also for signaling induced by cytokines. In addition, MAPKAP K2 and K3 phosphorylate and thus regulate heat shock proteins HSP 25 and HSP 27, which are involved in cytoskeletal reorganization.

Several small molecule inhibitors of p38 have been reported which inhibit IL-1 and TNF synthesis in human monocytes at concentrations in the low μM range [Lee, J. C. et al, Int. J. Immunopharm. 1988, 10, 835] and exhibit activity in animal models which are refractory to

cyclooxygenase inhibitors [Lee, J. C. et al, Annals N. Y. Acad. Sci. 1993, 696, 149]. In addition, these small molecule inhibitors are known to also decrease the synthesis of a wide variety of pro-inflammatory proteins including IL-6, IL-8, granulocyte/macrophage colony-stimulating factor (GM-CSF) and cyclooxygenase-2 (COX-2). TNF-induced phosphorylation and activation of cytosolic PLA2, TNF-induced expression of VCAM-1 on endothelial cells, and IL-1-stimulated synthesis of collagenase and stromelysin are also inhibited by such small molecule inhibitors of p38 [Cohen, P. Trends Cell Biol. 1997, 7, 353-61].

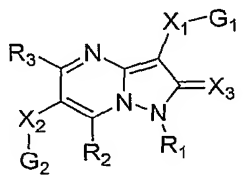
A variety of cells including monocytes and macrophages produce TNF and IL-1. Excessive or unregulated TNF production is implicated in a number of disease states including Crohn's disease, ulcerative colitis, pyresis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, toxic shock syndrome, endotoxic shock, sepsis, septic shock, gram negative sepsis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejection, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, cerebral malaria, scar tissue formation, keloid formation, fever and myalgias due to infection such as influenza, cachexia secondary to acquired immune deficiency syndrome (AIDS), cachexia secondary to infection or malignancy, AIDS or AIDS-related complex.

The central position that p38 occupies within the cascade of signaling molecules mediating extracellular-to-intracellular signaling, and its influence over not only IL-1, TNF and IL-8 production but also the synthesis and/or action of other pro-inflammatory proteins (e.g. IL-6, GM-CSF, COX-2, collagenase and stromelysin), make it an attractive target for inhibition by small molecule inhibitors with the expectation that such inhibition would be a highly effective mechanism for regulating the excessive and destructive activation of the immune system. Such an expectation is supported by the potent and diverse anti-inflammatory activities described for p38 kinase inhibitors [Adams, ibid; Badger, et al, J. Pham. Exp. Ther. 1996, 279, 1453-61; Griswold, et al, Pharmacol. Comm., 1996, 7, 323-29].

SUMMARY OF THE INVENTION

There are disclosed potent and selective inhibitors of p38 kinase and the isoforms and splice variants thereof, especially p38α and p38β. The compounds are useful in pharmaceutical compostions and their use to treat p38 related disease, for example in the prophylaxis and treatment of immune or inflammatory disorders as described herein.

The present invention discloses a class of compounds, useful in treating p38 kinase mediated disorders and conditions, defined by structural Formula I:



I

or a a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

X_1 and X_2 are independently selected from the group consisting of a bond, –O–, –NR_4–, alkenyl, alkynyl, –C(O)–, sulfanyl, sulfinyl, –SO_2–, –$SO_2N(R_4)$–, –$N(R_4)S(O)_2$–, –$C(R_5)_2$–, –$C(R_5)_2N(R_4)$–, $N(R_4)C(O)$–, –$C(O)N(R_4)$–, –$N(R_4)C(O)N(R_4)$–, and –OC(O)O–;

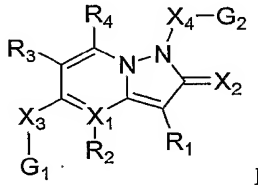
G_1 and G_2 are independently selected from the group consisting of aryl, cycloalkyl, heteroaryl, and heterocyclo, any of which may be optionally substituted;

X_3 is selected from the group consisting of oxygen or sulfur;

R_1, R_4, and R_5 are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylamino, alkylene, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkenyl, arylalkyl, arylalkynyl, arylcarbonyl, arylsulfonyl, cyanoalkenyl, cycloalkyl, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonyl, heterocycle, heterocycloalkenyl, heterocycloalkyl, and hydroxyalkyl; and

R^2 and R^3 are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, cyano, cyanoalkenyl, cycloalkyl, halo, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocycloalkenyl, heterocycloalkyl, hydroxy, hydroxyalkyl, and nitro.

Another class of compounds useful in treating p38 related disorders and conditions is defined by Formula II:



II

or a salt, ester, tautomer or prodrug thereof, wherein:

X^1 is selected from the group consisting of carbon or nitrogen;

X^2 is selected from the group consisting of oxygen or sulfur;

X^3 is selected from the group consisting of a bond, –O–, –NR^5–, alkylene, alkenylene, alkynylene, –C(O)–, –S–, –S(O)–, –SO_2–, –$SO_2N(R^5)$–, –$N(R^5)SO_2$–, –$C(R^6)_2N(R^5)$–, –$N(R^5)C(O)$–, –$C(O)N(R^5)$–, –$N(R^5)C(O)N(R^5)$–, and –OC(O)O–;

X^4 is selected from the group consisting of a bond, alkyl, –C(O)–, –SO_2–, –$N(R^5)SO_2$–, and –$N(R^5)C(O)$–;

G^1 and G^2 are independently selected from the group consisting of aryl, cycloalkyl, heteroaryl, and heterocyclo, any of which may be optionally substituted;

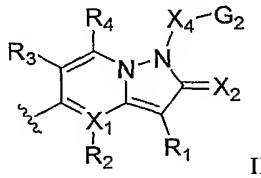
R^1 and R^6 are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylamino, alkylene, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkenyl, arylalkyl, arylalkynyl, arylcarbonyl, arylsulfonyl, cyanoalkenyl, cycloalkyl,

haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonyl, heterocycle, heterocycloalkenyl, heterocycloalkyl, and hydroxyalkyl;

R^2, R^3, and R^4 are independently absent or selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, cyano, cyanoalkenyl, cycloalkyl, halo, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocycloalkenyl, heterocycloalkyl, hydroxy, hydroxyalkyl, and nitro; and

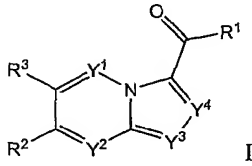
R^5 is selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylamino, alkylene, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkenyl, arylalkyl, arylalkynyl, arylcarbonyl, arylsulfonyl, cyanoalkenyl, cycloalkyl, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonyl, heterocycle, heterocycloalkenyl, heterocycloalkyl, hydroxyalkyl, any of which may be optionally substituted and Z, wherein

Z has the structural formula III:



III.

Yet another class of compounds useful in treating p38 related disorders and conditions is defined by Formula IV:



IV

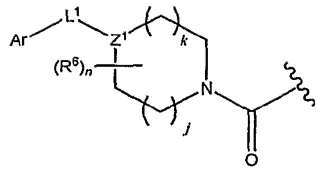
or the pharmaceutically acceptable salts thereof, wherein

Y^1, Y^2, Y^3 and Y^4 are each independently selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of acyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylcarbonyl, alkylthio, alkylthiocarbonyl, amino, aminoalkyl, amido, aryl, arylalkoxy, arylalkyl, arylalkylamino, arylalkylthio, arylamino, arylamido, aryloxy, arylthio, carboxy, cycloalkyl, cycloalkylcarbonyl, haloalkoxy, haloalkoxycarbonyl, haloalkyl, heteroaryl, heteroarylcarbonyl, heteroarylamino, heteroarylamido, heteroaryloxy, heteroarylthio, heterocyclo, heterocyclocarbonyl, hydroxy, and thiol;

R^2 is selected from the group consisting of hydrogen, acyl, alkoxy, alkoxyalkyl, alkyl, alkylamino, amino, amido, alkylamino, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and sulfonate;

R^3 is of the Formula V:



V;

Z^1 is selected from the group consisting of N and CR^4;

j, *k*, and *n* are independently selected to be from zero to four;

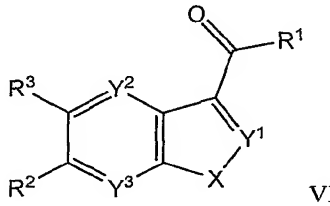
L^1 is selected from the group consisting of a bond, alkyl, $-C(O)-$, $-NR^5-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-C(O)O-$, $-OC(O)-$, $-N(R^5)C(O)-$, $-C(O)N(R^5)-$, $-N(R^5)C(O)O-$, $-N(R^5)C(O)N(R^5)-$, $-OC(O)N(R^5)-$, $-N(R^5)C(O)S-$, and $-OC(O)N(R^5)-$;

Ar is selected from the group consisting of aryl and heteroaryl;

each R^4 is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkyl, alkylamino, amido, amino, aminoalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and hydroxyalkyl; and

each R^5, and R^6 are independently selected from the group consisting of hydrogen, alkoxy, alkyl, halo, haloalkyl, hydroxy, and hydroxyalkyl.

Yet another class of compounds useful in treating p38 related disorders and conditions is defined by Formula VI:



VI

or therapeutically relevant derivative thereof, wherein

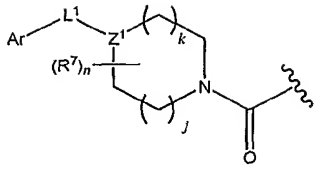
X is selected from the group consisting of $-O-$, $-NR^5-$, and $-S-$;

Y^1, Y^2, and Y^3 are each independently selected from the group consisting of CR^6 and N;

R^1 is selected from the group consisting of acyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylcarbonyl, alkylthio, alkylthiocarbonyl, amino, aminoalkyl, amido, aryl, arylalkoxy, arylalkyl, arylalkylamino, arylalkylthio, arylamino, arylamido, aryloxy, arylthio, carboxy, cycloalkyl, cycloalkylcarbonyl, haloalkoxy, haloalkoxycarbonyl, haloalkyl, heteroaryl, heteroarylcarbonyl, heteroarylamino, heteroarylamido, heteroaryloxy, heteroarylthio, heterocyclo, heterocyclocarbonyl, hydroxy, and thiol;

R^2 is selected from the group consisting of hydrogen, acyl, alkoxy, alkoxyalkyl, alkyl, alkylamino, amino, amido, alkylamino, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and sulfonate;

R^3 is of Formula VII



VII;

Z^1 is selected from the group consisting of N and CR^4;

j, *k*, and *n* are independently selected to be from zero to four;

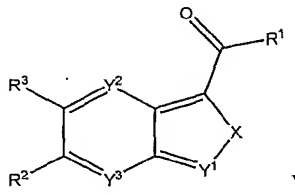
L^1 is selected from the group consisting of a bond, alkyl, –C(O)–, $–NR^5–$, –O–, –S–, –S(O)–, $–SO_2–$, –C(O)O–, –OC(O)–, $–N(R^5)C(O)–$, $–C(O)N(R^5)–$, $–N(R^5)C(O)O–$, $–N(R^5)C(O)N(R^5)–$, $–OC(O)N(R^5)–$, $–N(R^5)C(O)S–$, and $–OC(O)N(R^5)–$;

Ar is selected from the group consisting of aryl and heteroaryl;

each R^4 is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkyl, alkylamino, amido, amino, aminoalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and hydroxyalkyl; and

each R^5, R^6, and R^7 are independently selected from the group consisting of hydrogen, alkoxy, alkyl, halo, haloalkyl, hydroxy, and hydroxyalkyl.

Yet another class of compounds useful in treating p38 related disorders and conditions is defined by Formula VIII:



VIII

or therapeutically relevant derivative thereof, wherein

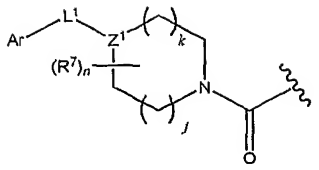
X is selected from the group consisting of –O–, $–NR^5–$, and –S—;

Y^1, Y^2, and Y^3 are each independently selected from the group consisting of CR^6 and N;

R^1 is selected from the group consisting of acyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylcarbonyl, alkylthio, alkylthiocarbonyl, amino, aminoalkyl, amido, aryl, arylalkoxy, arylalkyl, arylalkylamino, arylalkylthio, arylamino, arylamido, aryloxy, arylthio, carboxy, cycloalkyl, cycloalkylcarbonyl, haloalkoxy, haloalkoxycarbonyl, haloalkyl, heteroaryl, heteroarylcarbonyl, heteroarylamino, heteroarylamido, heteroaryloxy, heteroarylthio, heterocyclo, heterocyclocarbonyl, hydroxy, and thiol;

R^2 is selected from the group consisting of hydrogen, acyl, alkoxy, alkoxyalkyl, alkyl, alkylamino, amino, amido, alkylamino, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and sulfonate;

R^3 is of the Formula IX



IX;

Z^1 is selected from the group consisting of N and CR^4;

j, *k*, and *n* are independently selected to be from zero to four;

L^1 is selected from the group consisting of a bond, alkyl, –C(O)–, $–NR^5–$, –O–, –S–, –S(O)–, $–SO_2–$, –C(O)O–, –OC(O)–, $–N(R^5)C(O)–$, $–C(O)N(R^5)–$, $–N(R^5)C(O)O–$, $–N(R^5)C(O)N(R^5)–$, $–OC(O)N(R^5)–$, $–N(R^5)C(O)S–$, and $–OC(O)N(R^5)–$;

Ar is selected from the group consisting of aryl and heteroaryl;

each R^4 is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkyl, alkylamino, amido, amino, aminoalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and hydroxyalkyl; and

each R^5, R^6, and R^7 are independently selected from the group consisting of hydrogen, alkoxy, alkyl, halo, haloalkyl, hydroxy, and hydroxyalkyl.

Compounds according to the present invention possess useful p38 inhibiting or modulating activity, and may be used in the treatment or prophylaxis of a disease or condition in which p38 plays an active role. Thus, in broad aspect, the present invention also provides pharmaceutical compositions comprising one or more compounds of the present invention together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. In certain embodiments, the present invention provides methods for inhibiting / modulating p38. In other embodiments, the present invention provides methods for treating a p38 mediated disorder in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of a compound or composition according to the present invention. The present invention also contemplates the use of compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the inhibition / modulation of p38.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the terms below have the meanings indicated.

The term "acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $–C(O)CH_3$ group. Examples of acyl groups include formyl, alkanoyl and aroyl radicals.

The term "acylamino" embraces an amino radical substituted with an acyl group. An example of an "acylamino" radical is acetylamino ($CH_3C(O)NH–$).

The term "alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20,

preferably 2 to 6, carbon atoms. Alkenylene refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(–CH=CH–),(–C::C–)]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like.

The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

The term "alkoxyalkoxy," as used herein, alone or in combination, refers to one or more alkoxy groups attached to the parent molecular moiety through another alkoxy group. Examples include ethoxyethoxy, methoxypropoxyethoxy, ethoxypentoxyethoxyethoxy and the like.

The term "alkoxyalkyl," as used herein, alone or in combination, refers to an alkoxy group attached to the parent molecular moiety through an alkyl group. The term "alkoxyalkyl" also embraces alkoxyalkyl groups having one or more alkoxy groups attached to the alkyl group, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups.

The term "alkoxycarbonyl," as used herein, alone or in combination, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group. Examples of such "alkoxycarbonyl" groups include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. More preferred alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl.

The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to and including 20, preferably 1 to 10, and more preferably 1 to 6, carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene ($–CH_2–$).

The term "alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "alkylaminocarbonyl" as used herein, alone or in combination, refers to an alkylamino group attached to the parent molecular moiety through a carbonyl group. Examples of such radicals include N-methylaminocarbonyl and N,N-dimethylcarbonyl.

The term "alkylcarbonyl" and "alkanoyl," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl.

The term "alkylidene," as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

The term "alkylsulfinyl," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a sulfinyl group. Examples of alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

The term "alkylsulfonyl," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group. Examples of alkylsulfinyl groups include methanesulfonyl, ethanesulfonyl, tert-butanesulfonyl, and the like.

The term "alkylthio," as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as defined above. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, ethoxyethylthio, methoxypropoxyethylthio, ethoxypentoxyethoxyethylthio and the like.

The term "alkylthioalkyl" embraces alkylthio radicals attached to an alkyl radical. Alkylthioalkyl radicals include "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms and an alkylthio radical as described above. Examples of such radicals include methylthiomethyl.

The term "alkynyl," as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20, preferably from 2 to 6, more preferably from 2 to 4, carbon atoms. "Alkynylene" refers to a carbon-carbon triple bond attached at two positions such as ethynylene (–C:::C–, –C≡C–). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl, and the like.

The term "amido," as used herein, alone or in combination, refers to an amino group as described below attached to the parent molecular moiety through a carbonyl group. The term "C-amido" as used herein, alone or in combination, refers to a -C(=O)-NR_2 group with R as defined herein. The term "N-amido" as used herein, alone or in combination, refers to a RC(=O)NH- group, with R as defined herein.

The term "amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocycloalkenyl, and heterocycloalkyl, wherein the aryl, the aryl part of the arylalkenyl, the arylalkyl, the heteroaryl, the heteroaryl part of the heteroarylalkenyl and the heteroarylalkyl, the heterocycle, and the heterocycle part of the heterocycloalkenyl and the heterocycloalkyl can be optionally substituted as defined herein with one, two, three, four, or five substituents.

The term "aminoalkyl," as used herein, alone or in combination, refers to an amino group attached to the parent molecular moiety through an alkyl group. Examples include aminomethyl, aminoethyl and aminobutyl.

The terms "aminocarbonyl" and "carbamoyl," as used herein, alone or in combination, refer to an amino-substituted carbonyl group, wherein the amino group can be a primary or secondary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

The term "aminocarbonylalkyl," as used herein, alone or in combination, refers to an aminocarbonyl radical attached to an alkyl radical, as described above. An example of such radicals is aminocarbonylmethyl. The term "amidino" denotes an $-C(NH)NH_2$ radical. The term "cyanoamidino" denotes an $-C(N-CN)NH_2$ radical.

The term "aralkenyl" or "arylalkenyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

The term "aralkoxy" or "arylalkoxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term "aralkyl" or "arylalkyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

The term "aralkylamino" or "arylalkylamino," as used herein, alone or in combination, refers to an arylalkyl group attached to the parent molecular moiety through a nitrogen atom, wherein the nitrogen atom is substituted with hydrogen.

The term "aralkylidene" or "arylalkylidene," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkylidene group

The term "aralkylthio" or "arylalkylthio," as used herein, alone or in combination, refers to an arylalkyl group attached to the parent molecular moiety through a sulfur atom.

The term "aralkynyl" or "arylalkynyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

The term "aralkoxycarbonyl," as used herein, alone or in combination, refers to a radical of the formula aralkyl-O–C(O)– in which the term "aralkyl," has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl (Z or Cbz) and 4-methoxyphenylmethoxycarbonyl (MOS).

The term "aralkanoyl," as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like. The term "aroyl" refers to an acyl radical derived from an arylcarboxylic acid, "aryl" having the meaning given below. Examples of such aroyl radicals include substituted and unsubstituted benzoyl or napthoyl such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-

2-naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like.

The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as benzyl, phenyl, naphthyl, anthracenyl, phenanthryl, indanyl, indenyl, annulenyl, azulenyl, tetrahydronaphthyl, and biphenyl.

The term "arylamino" as used herein, alone or in combination, refers to an aryl group attached to the parent moiety through an amino group, such as methylamino, N-phenylamino, and the like.

The terms "arylcarbonyl" and "aroyl," as used herein, alone or in combination, refer to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "aryloxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

The term "arylsulfonyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The term "arylthio," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through a sulfur atom.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes --CO_2H.

The terms "benzo" and "benz," as used herein, alone or in combination, refer to the divalent radical C_6H_4= derived from benzene. Examples include benzothiophene and benzimidazole.

The term "O-carbamyl" as used herein, alone or in combination, refers to a -OC(O)NRR', group-with R and R' as defined herein.

The term "N-carbamyl" as used herein, alone or in combination, refers to a ROC(O)NR'- group, with R and R' as defined herein.

The term "carbonyl," as used herein, when alone includes formyl [–C(O)H] and in combination is a –C(O)– group.

The term "carboxy," as used herein, refers to –C(O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-carboxy" group refers to a RC(O)O– group, where R is as defined herein. A "C-carboxy" group refers to a –C(O)OR groups where R is as defined herein.

The term "cyano," as used herein, alone or in combination, refers to –CN.

The term "cycloalkyl," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from 3 to 12, preferably five to seven, carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydonapthalene, octahydronapthalene as well as the multicyclic

(multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by bicyclo[2,2,2]octane, bicyclo[2,2,2]octane, bicyclo[1,1,1]pentane, camphor and bicyclo[3,2,1]octane.

The term "ester," as used herein, alone or in combination, refers to a carboxyl group bridging two moieties linked at carbon atoms.

The term "ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a halohydrocarbyl group attached at two or more positions. Examples include fluoromethylene (–CFH–), difluoromethylene ($–CF_2–$), chloromethylene (–CHCl–) and the like.

The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, -CH2-NH-OCH3.

The term "heteroaryl," as used herein, alone or in combination, refers to 3 to 7 membered, preferably 5 to 7 membered, unsaturated heterocyclic rings wherein at least one atom is selected from the group consisting of O, S, and N. Heteroaryl groups are exemplified by: unsaturated 3 to 7 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.]tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo[1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic

groups containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.]etc.; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.]and isothiazolyl; unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.]and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuryl, benzothienyl, and the like.

The term "heteroaralkenyl" or "heteroarylalkenyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkenyl group.

The term "heteroaralkoxy" or "heteroarylalkoxy," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkoxy group.

The term "heteroarylalkyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkyl group.

The term "heteroaralkylidene" or "heteroarylalkylidene," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkylidene group.

The term "heteroaryloxy," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an oxygen atom.

The term "heteroarylsulfonyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through a sulfonyl group.

The terms "heterocycloalkyl" and, interchangeably, "heterocycle," as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic radical containing at least one, preferably 1 to 4, and more preferably 1 to 2 heteroatoms as ring members, wherein each said heteroatom may be independently selected from the group consisting of nitrogen, oxygen, and sulfur, and wherein there are preferably 3 to 8 ring members in each ring, more preferably 3 to 7 ring members in each ring, and most preferably 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Heterocycle groups of the invention are exemplified by aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl,

pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

The term "heterocycloalkylalkenyl," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular moiety through an alkenyl group.

The term "heterocycloalkylalkoxy," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular group through an oxygen atom.

The term "heterocycloalkylalkylidene," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular moiety through an alkylidene group.

The term "hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., –N–N–.

The term "hydroxy," as used herein, alone or in combination, refers to –OH.

The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

The term "imino," as used herein, alone or in combination, refers to =N–.

The term "iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N–O–.

The phrase "in the main chain" refers to the longest contiguous or adjacent chain of carbon atoms starting at the point of attachment of a group to the compounds of this invention.

The term "isocyanato" refers to a –NCO group.

The term "isothiocyanato" refers to a –NCS group.

The phrase "linear chain of atoms" refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

The term "lower," as used herein, alone or in combination, means containing from 1 to and including 6 carbon atoms.

The term "mercaptoalkyl" as used herein, alone or in combination, refers to an R'SR– group, where R and R' are as defined herein.

The term "mercaptomercaptyl" as used herein, alone or in combination, refers to a RSR'S– group, where R is as defined herein.

The term "mercaptyl" as used herein, alone or in combination, refers to an RS– group, where R is as defined herein.

The term "nitro," as used herein, alone or in combination, refers to $–NO_2$.

The terms "oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

The term "oxo," as used herein, alone or in combination, refers to =O.

The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer the $-SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

The term "sulfanyl," as used herein, alone or in combination, refers to –S–.

The term "sulfinyl," as used herein, alone or in combination, refers to –S(O)–.

The term "sulfonyl," as used herein, alone or in combination, refers to $-SO_2-$.

The term "N-sulfonamido" refers to a $RS(=O)_2NR'$- group with R and R' as defined herein.

The term "S-sulfonamido" refers to a $-S(=O)_2NRR'$, group, with R and R' as defined herein.

The terms "thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

The term "thiol," as used herein, alone or in combination, refers to an –SH group.

The term "thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

The term "N-thiocarbamyl" refers to an ROC(S)NR'– group, with R and R'as defined herein.

The term "O-thiocarbamyl" refers to an –OC(S)NRR' group, with R and R' as defined herein.

The term "thiocyanato" refers to a –CNS group.

The term "trihalomethanesulfonamido" refers to a $X_3CS(O)_2NR-$ group with X is a halogen and R as defined herein.

The term "trihalomethanesulfonyl" refers to a $X_3CS(O)_2-$ group where X is a halogen.

The term "trihalomethoxy" refers to a X_3CO- group where X is a halogen.

The term "trisubstituted silyl," as used herein, alone or in combination, refers to a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethysilyl, tert-butyldimethylsilyl, triphenylsilyl and the like.

When a group is defined to be "null," what is meant is that said group is absent.

The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, arylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylsulfinyl, arylsulfonyl, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-menbered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., -

CH_2CH_3), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particuar moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety selected from the group consisting of hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R^n where n=(1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. Thus, by way of example only, an unsymmetrical group such as $-C(O)N(R^5)-$ may be attached to the parent moiety at either the carbon or the nitrogen.

Asymmetric centers exist in the compounds of the present invention. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms,as well as d-isomers and l-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified.

The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

"p38 kinase inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to p38 kinase activity of no more than about 100 .mu.M and more typically not more than about 50 μM, as measured in the p38α Assay described generally hereinbelow. "IC_{50}" is that concentration of inhibitor which reduces the activity of an enzyme (e.g., p38 kinase) to half-maximal level. Representative compounds of the present invention have been discovered to exhibit inhibitory activity against p38 kinase. Compounds of the present invention preferably exhibit an IC_{50} with respect to p38 kinase of no more than about 10 μM, more preferably, no more than about 5 μM, even more preferably not more than about 1 μM, and most preferably, not more than about 200 nM, as measured in the p38 kinase assay(s) described herein.

The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of atherosclerosis. This amount will achieve the goal of reducing or eliminating the hyperlipidemic condition.

The term "prodrug" refers to a compound that is made more active in vivo. The present compounds can also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound. The term "therapeutically acceptable prodrug," refers to those prodrugs or zwitterions which are suitable for

use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis. The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible; which are suitable for treatment of diseases without undue toxicity, irritation, and allergic-response; which are commensurate with a reasonable benefit/risk ratio; and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds of the compounds of the present invention and the like.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

The compounds of the present invention can exist as therapeutically acceptable salts. The present invention includes compounds listed above in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, the subject invention provides a pharmaceutical formulation comprising a compound or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences. The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients.

Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an

acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

Compounds of the present invention may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present invention externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

Gels for topical or transdermal administration of compounds of the subject invention may comprise, generally, a mixture of volatile solvents, nonvolatile solvents, and water. The volatile solvent component of the buffered solvent system may preferably include lower (C1-C6) alkyl alcohols, lower alkyl glycols and lower glycol polymers. More preferably, the volatile solvent is ethanol. The volatile solvent component is thought to act as a penetration enhancer, while also producing a cooling effect on the skin as it evaporates. The nonvolatile solvent portion of the buffered solvent system is selected from lower alkylene glycols and lower glycol polymers. Preferably, propylene glycol is used. The nonvolatile solvent slows the evaporation of the volatile solvent and reduces the vapor pressure of the buffered solvent system. The amount of this nonvolatile solvent component, as with the volatile solvent, is determined by the pharmaceutical compound or drug being used. When too little of the nonvolatile solvent is in the system, the pharmaceutical compound may crystallize due to evaporation of volatile solvent, while an excess will result in a lack of bioavailability due to poor release of drug from solvent mixture. The buffer component of the buffered solvent system may be selected from any buffer commonly used in the art; preferably, water is used. The preferred ratio of ingredients is about 20% of the nonvolatile solvent, about 40% of the volatile solvent, and about 40% water. There are several optional ingredients which can be added to the topical composition. These include, but are not limited to, chelators and gelling agents. Appropriate gelling agents can include, but are not limited to, semisynthetic cellulose derivatives (such as hydroxypropylmethylcellulose) and synthetic polymers, and cosmetic agents.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit

dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The compounds of the invention may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The compounds of the subject invention can be administered in various modes, *e.g.* orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

Specific, non-limiting examples of possible combination therapies include use of the compounds of the invention with agents found in the following pharmacotherapeutic classifications as indicated below. These lists should not be construed to be closed, but should instead serve as illustrative examples common to the relevant therapeutic areaat present. Moreover, combination regimens may include a variety of routes of administration and should include intravenous, intraocular, subcutaneous, dermal, inhaled topical, oral.

For the treatment of inflammatory pain, compounds according to the present invention may be administered with an agent selected from the group comprising: a) corticosteroids including betamethasone dipropionate (augmented and nonaugemnted), betamethasone valerate, clobetasol propionate, prednisone, methyl prednisolone, diflorasone diacetate, halobetasol propionate, amcinonide, dexamethasone, dexosimethasone, fluocinolone acetononide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, and flurandrenalide; b) non-steroidal anti-inflammatory drugs including salicylates, ibuprofen, ketoprofen, etodolac, diclofenac, meclofenamate sodium, naproxen, piroxicam, and celecoxib; c) muscle relaxants and combinations thereof with other agents, including cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, and cyclobenzaprine/lidocaine/ketoprofen; d) anaesthetics and combinations thereof with other agents, including lidocaine, lidocaine/deoxy-D-glucose (an antiviral), prilocaine, and EMLA Cream [Eutectic Mixture of Local Anesthetics (lidocaine 2.5% and prilocaine 2.5%; an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather then as crystals)]; i) opioids including codeine, loperamide, tramadol, morphine, fentanyl, oxycodone, hydrocodone, levorphanol, and butorphanol; j) topical counter-irritants including menthol, oil of wintergreen, camphor, eucalyptus oil and turpentine oil; k) topical cannabinoids including selective and

non-selective CB1/CB2 ligands; l) agents with analgesic and antipyretic properties including acetaminophen; m) agents that modify inflammatory mediators including infliximab; n) nitric oxide synthase inhibitors, particularly inhibitors of inducible nitric oxide stnthase; and other agents, such as capsaicin.

For the treatment of autoimmune disorders, compounds according to the present invention may be administered with an agent selected from the group comprising: corticosteroids including dexamethasome, prednisone, and methylprednisolone; immunosuppressant agents including azathioprine, cyclosporine, and immunoglobulins; and prostaglandin analogs including latanoprost, travoprost, bimatoprost, and unoprostone; prostaglandin analogs that modify inflammatory mediators including infliximab and rutuximab; and antimetabolites including methotrexate.

For the treatment of respiratory disorders, compounds according to the present invention may be administered with an agent selected from the group comprising: sympathomimetic agents including salmeterol, albuterol, terbutaline, metaproterenol, and ipratropium bromide; and mast cell stabilizers including cromolyn.

For the treatment of endocrine disorders, compounds according to the present invention may be administered with an agent selected from the group comprising: insulin and insulin derivatives; sulfonylureas agents including glimepiride and glipizide; biguanide agents including metformin; and PPAR modulators such as thiazolidnedione agents including pioglitazone and rosigliatzone.

For the treatment of oncologic diseases, proliferative disorders, and cancers, compounds according to the present invention may be administered with an agent selected from the group comprising: aromatase inhibitors, antiestrogen, anti-androgen, or gonadorelin agonists, topoisomerase 1and 2 inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, or platin containing compounds, lipid or protein kinase targeting agents, protein or lipid phosphatase targeting agents, anti-angiogentic agents, agents that induce cell differentiation, bradykinin 1 receptor antagonists, angiotensin II antagonists, cyclooxygenase inhibitors, heparanase inhibitors, lymphokines or cytokine inhibitors, bisphosphanates, rapamycin derivatives, anti-apoptotic pathway inhibitors, apoptotic pathway agonists, inhibitors of Ras isoforms, telomerase inhibitors, protease inhibitors, metalloproteinase inhibitors, and aminopeptidase inhibitors.

For the treatment of ophthalmologic disorders and diseases of the eye, compounds according to the present invention may be administered with an agent selected from the group comprising: beta-blockers including timolol, betaxolol, levobetaxolol, carteolol, levobunolol, and propranolol; carbonic anhydrase inhibitors including brinzolamide and dorzolamide; α- and β-adrenergic antagonists including α1-adrenergic antagonists such as nipradilol and α2 agonists such as iopidine and brimonidine; miotics including pilocarpine and epinephrine; prostaglandin analogs including latanoprost, travoprost, bimatoprost, and unoprostone; corticosteroids including dexamethasone, prednisone, and methylprednisolone; and immunosuppressant agents including azathioprine, cyclosporine, and immunoglobulins.

In any case, the multiple therapeutic agents (at least one of which is a compound of the present invention) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

Thus, in another aspect, the present invention provides methods for treating p38 kinase mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of the present invention effective to reduce or prevent said disorder in the subject in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, the present invention provides therapeutic compositions comprising at least one compound of the present invention in combination with one or more additional agents for the treatment of p38 kinase mediated disorders.

The invention also extends to the prophylaxis or treatment of any disease or disorder in which p38 kinase plays a role including conditions caused by excessive or unregulated pro-inflammatory cytokine production including for example excessive or unregulated TNF, IL-1, IL-6 and IL-8 production in a human, or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such cytokine-mediated diseases or disorders. Further, the invention extends to the administration to a human an effective amount of a p38 inhibitor for treating any such disease or disorder.

Diseases or disorders in which p38 kinase plays a role, either directly or via pro-inflammatory cytokines including the cytokines TNF, IL-1, IL-6 and IL-8, include, without limitation: autoimmune diseases, inflammatory diseases, destructive-bone disorders, proliferative disorders, neurodegenerative disorders, viral diseases, allergies, infectious diseases, heart attacks, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation, and conditions associated with prostaglandin endoperoxidase synthetase-2 (COX-2).

Autoimmune diseases which may be prevented or treated include, but are not limited to: rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs. host disease, or psoriasis.

The invention further extends to the particular autoimmune disease rheumatoid arthritis.

Inflammatory diseases which may be prevented or treated include, but are not limited to: asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis.

In addition, p38 inhibitors of this invention also exhibit inhibition of expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxidase synthetase-2, otherwise known as cyclooxygenase-2 (COX-2) and are therefore of use in therapy. Pro-inflammatory mediators of the

cyclooxygenase pathway derived from arachidonic acid are produced by inducible COX-2 enzyme. Regulation of COX-2 would regulate these pro-inflammatory mediators such as prostaglandins, which affect a wide variety of cells and are important and critical inflammatory mediators of a wide variety of disease states and conditions. In particular, these inflammatory mediators have been implicated in pain, such as in the sensitization of pain receptors, or edema. Accordingly, additional p38 mediated conditions which may be prevented or treated include edema, analgesia, fever and pain such as neuromuscular pain, headache, dental pain, arthritis pain and pain caused by cancer.

As a result of their p38 inhibitory activity, compounds of the invention have utility in the prevention and treatment of diseases associated with cytokine production including but not limited to those diseases associated with TNF, IL-1, IL-6 and IL-8 production.

Besides being useful for human treatment, the compounds and formulations of the present invention are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

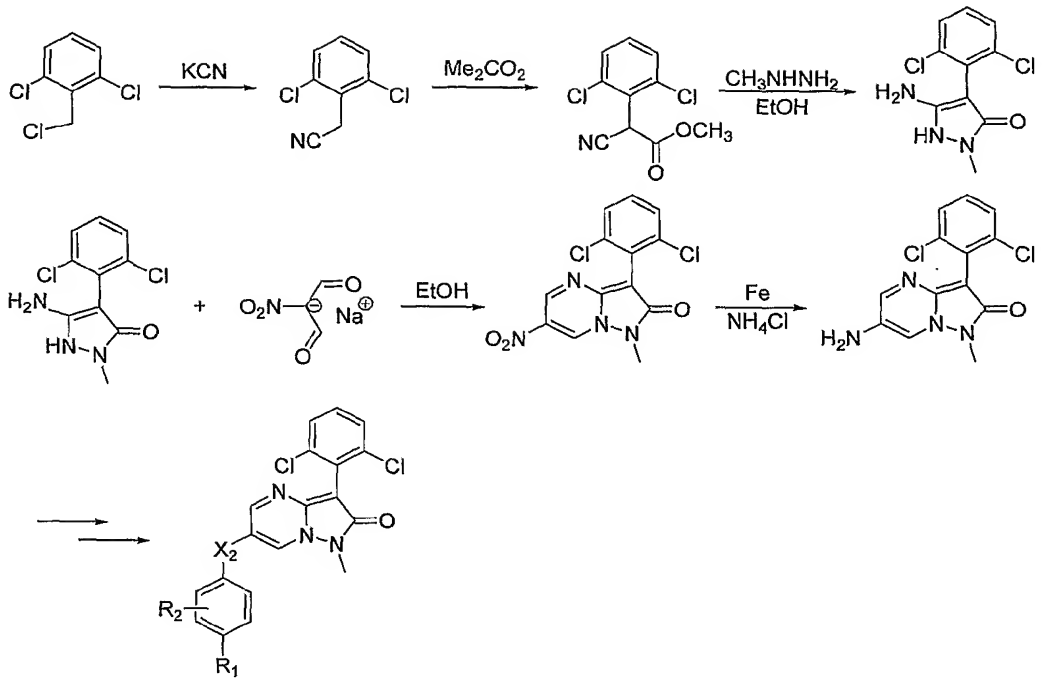
All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein.

GENERAL SYNTHETIC METHODS FOR PREPARING COMPOUNDS

Molecular embodiments of the present invention can be synthesized using standard synthetic techniques known to those of skill in the art. Compounds of the present invention can be synthesized using the general synthetic procedures set forth in Schemes I-II.

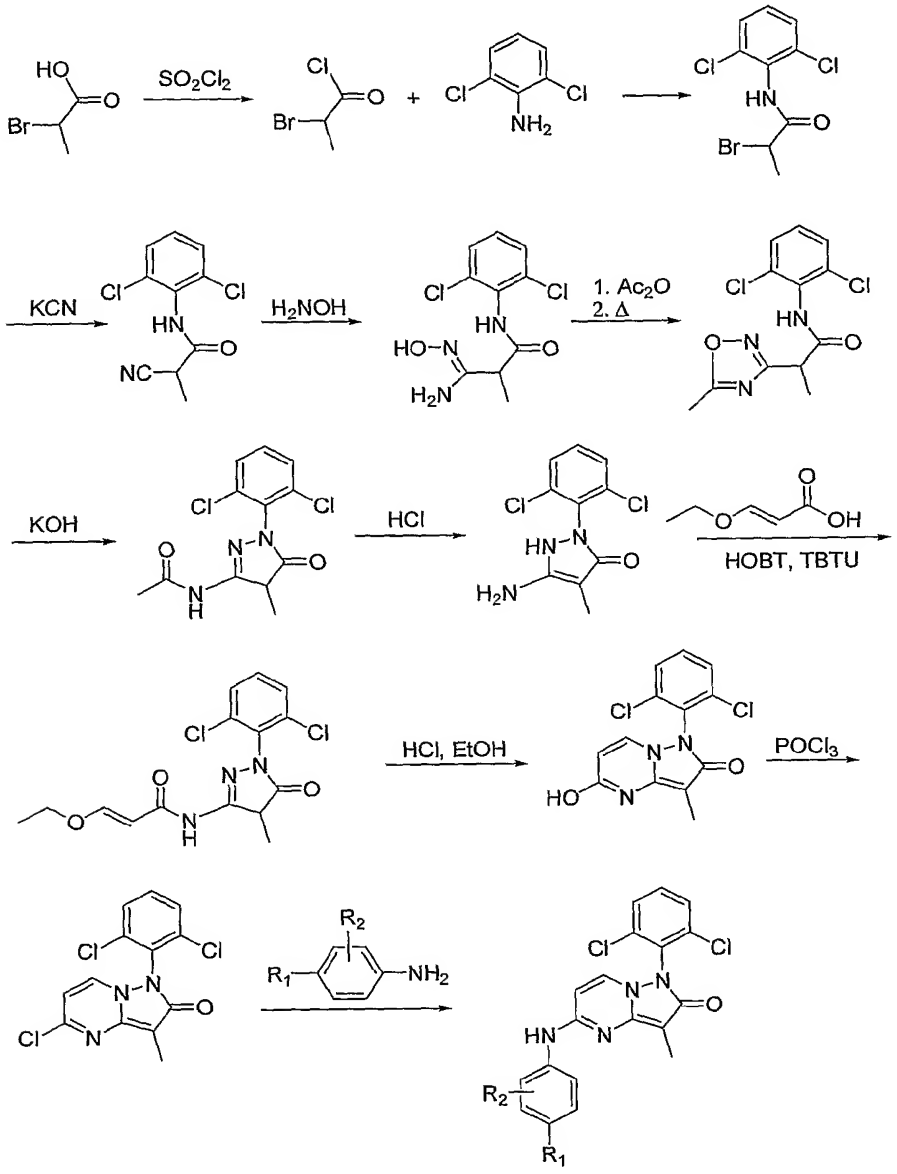
Examples 1-3 can be synthesized using the synthetic procedure set forth in Scheme I.

SCHEME I


KCN
Me2CO2
CH3NHNH2
EtOH
EtOH
Fe
NH4Cl

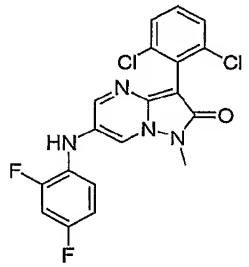
Examples 4-6 can be synthesized using the synthetic procedure set forth in Scheme I.

SCHEME II



The invension is further illustrated by the following examples.

EXAMPLE 1



3-(2,6-Dichloro-phenyl)-6-(2,4-difluoro-phenylamino)-1-methyl-pyrazolo[1,5-a]pyrimidin-2-one:

Step 1

(2,6-Dichlorophenyl)-acetonitrile: A 500 mL round-bottom flask was charged with a solution of KCN (26 g, 400.00 mmol) ,18-crown-6 (0.05 g) in water (60 ml). To this was added 1,3-dichloro-2-(chloromethyl)benzene (40 g, 206.24 mmol) in ethanol (300 ml). The resulting solution was allowed to stir for 1~3 hours while the temperature was maintained at reflux. The reaction progress was monitored by TLC (AcOEt: PE=1:4). The mixture was the concentrated to dryness on a rotary evaporator. The resulting residue was the transferred into a seperatory funnel, washed with water (5 x 100 mL) to afford 35.4 g (95%) of 2-(2,6-dichlorophenyl)acetonitrile as a white solid. This product was used without further purification.

Step 2

2-Cyano-(2,6-dichlorophenyl)-acetic acid methyl ester: A 500 mL round-bottom flask was charged with absolute methanol (100 mL) and sodium (6.2 g, 269.57 mmol). After all of sodium was dissolved, the mixture was evaporated to dryness. Then, 30 mL tolune was added and the mixture was dried down again by evaperation to give fresh NaOMe. To this was added dimethyl carbonate (300 mL) and 2-(2,6-dichlorophenyl)acetonitrile (25 g, 134.41 mmol). The resulting solution was allowed to reflux for 2 hours. The reaction progress was monitored by TLC (AcOEt: PE=1:4). The mixture was quenched by the addition of of 100 mL ice H_2O. Then, the pH was adjusted to ca. 6 by the addition of AcOH . The resulting mixture was then extracted with EtOAc (3 x 100 ml). Combined organic layers were then concentrated down in vacuo to afford a residue that was purified by a column chromatography eluted with a 20:1 PE / AcOEt. This resulted in 27.8 g (85%) of methyl 2-cyano-2-(2,6-dichlorophenyl)acetate as a white solid. This was used for next step without further purification.

Step 3

5-Amino-4-(2,6-dichlorophenyl)-2-methyl-1,2-dihydro-pyrazol-3-one: A 50 ml round-bottom flask was charged with a solution of cyano-(2,6-dichlorophenyl)-acetic acid methyl ester (1.05 g, 4.30 mmol)

in ethanol (20 ml). To the mixture was added 1-methylhydrazine (2 g, 43.48 mmol). The resulting solution was allowed to reflux for 48 hours. The reaction was monitored by TLC (CH_2Cl_2: CH_3OH = 10:1). Then, it was concentrated down on a rotary evaporator. The product was recrystallized from 4:1 PE:AcOEt to afford 0.3 g (23%) of 5-Amino-4-(2,6-dichlorophenyl)-2-methyl-1,2-dihydro-pyrazol-3-one as a white solid.

Step 4

3-(2,6-Dichloro-phenyl)-1-methyl-6-nitro-pyrazolo[1,5-a]pyrimidin-2-one: A 250 mL 3-necked round bottom flask was charged with a solution of sodium nitrite (50.84 g, 736.81 mmol) in H_2O (50 ml) followed by the addition of (E)-2,3-dibromo-4-oxobut-2-enoic acid (50 g, 193.90 mmol) in EtOH (50 mL) dropwise while rising the temperature to 54 °C over a time period of 90 minutes. The resulting solution was allowed to stir at this temperature for an additional 30 minutes. The reaction was monitored by TLC (CH_2Cl_2/MeOH = 10:1). The reaction mixture was cooled in a bath of ice/salt. The resulting precipitate was filtered off and redissolved in 300 mL of EtOH. The mixture was filtered off again. The filtrate was concentrated in vacuo to afford 15 g (49%) of sodium nitromalonaldehyde monohydrate as a yellow solid. This solid material (910 mg, 5.79 mmol) was charged into a 100 mL round bottom flask followed by addition of amino-4-(2,6-dichlorophenyl)-2-methyl-1,2-dihydro-pyrazol-3-one (750 mg, 2.91 mmol) in EtOH (30 mL). The resulting solution was allowed to reflux for overnight. The reaction progress was monitored by TLC (CH_2Cl_2/MeOH = 10:1). The mixture was concentrated in vacuo to afford a residue that was purified by column chromatography eluted with 50:1 CH_2Cl_2/MeOH to give 50 mg (5%) of 3-(2,6-dichlorophenyl)-1-methyl-6-nitro-pyrazolo[1,5-a]pyrimidin-2-one as a yellow solid. ^{1}H NMR (d_6-DMSO) δ: 9.07-9.75 (dd, 2H), 7.46-7.60 (m, 3H), 3.78 (s, 3H).

Step 5

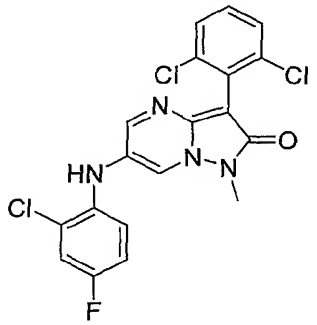
6-Amino-3-(2,6-dichloro-phenyl)-1-methyl-pyrazolo[1,5-a]pyrimidin-2-one: A 100 mL sealed tube was charged with a solution of 3-(2,6-dichloro-phenyl)-1-methyl-6-nitro-pyrazolo[1,5-a]pyrimidin-2-one (110 mg, 0.32 mmol) in CH_3OH (30 mL). To this was added iron (900 mg, 16.12 mmol) followed by the addition of a solution of ammonium chloride (870 mg, 16.26 mmol) in H_2O (10 mL). The resulting mixture was heated to 80 oC for 1 hour. The reaction progress was monitored by TLC (CH_2Cl_2/MeOH = 10:1). The mixture was filtered off and the filtrate was concentrated in vacuo. The residue was purified by eluting a column chromatography eluted with a 100:1 CH_2Cl_2/MeOH to afford 70 mg (70%) of 6-amino-3-(2,6-dichloro-phenyl)-1-methyl-pyrazolo[1,5-a]pyrimidin-2-one as a yellow solid. ^{1}H NMR ($CDCl_3$) δ: 8.02-8.26 (m, 2H), 7.28-7.47 (m, 3H), 3.54(s, 3H).

Step 6

3-(2,6-Dichloro-phenyl)-6-(2,4-difluoro-phenylamino)-1-methyl-pyrazolo[1,5-a]pyrimidin-2-one: To a solution of 6-amino-3-(2,6-dichloro-phenyl)-1-methyl-pyrazolo[1,5-a]pyrimidin-2-one (50 mg,

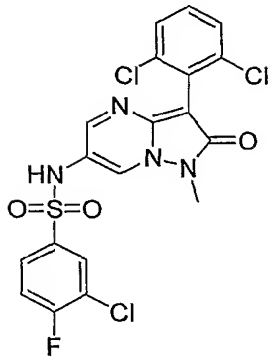
0.16 mmol) in MeOH(8 mL) was added 2,4-difluorophenylboronic acid (64 mg, 0.40 mmol) followed by CuI (6 mg, 0.032 mmol). The resulting mixture was allowed to stir at room temperature for 24 h. Then additional boronic acid (64 mg, 0.40 mmol) and CuI (6mg, 0.032 mmol) were added. The resulting mixture was allowed to stir at room temperature for 48 h. The reaction was monitored by TLC. The mixture was rinsed into a seperatory funnel with water and extratcted with EtOAc (3 x 10 mL), combined organics were washed with water (1 x 10 mL), brine (1 x10 mL) and dried over Na_2SO_4. It was filtered off and concentrated in vacuo to give the crude that was purified by reversed-phase C-18 column eluted with 20-60% CH_3CN in water in the presence of 0.1% TFA to afford 3 mg of 2,6-dichloro-phenyl)-6-(2,4-difluoro-phenylamino)-1-methyl-pyrazolo[1,5-a]pyrimidin-2-one. ^1H NMR ($CDCl_3$) δ: 8.44 (d, 1H), 8.05 (br, 1H), 7.88 (d, 1H), 7.42-7.40 (m, 1H), 7.27-7.23 (m, 2H), 7.00-6.85 (m, 2H), 3.79 (s, 3H); LCMS: 421.29 $(M)^+$.

EXAMPLE 2



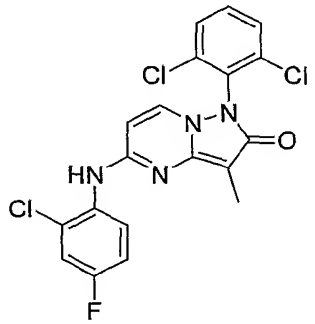
6-(2-Chloro-4-fluoro-phenylamino)-3-(2,6-dichloro-phenyl)-1-methyl-pyrazolo[1,5-a]pyrimidin-2-one: To a solution 6-amino-3-(2,6-dichloro-phenyl)-1-methyl-pyrazolo[1,5-a]pyrimidin-2-one (50 mg, 0.16 mmol) from step 5 of Example 1 in toluene (0.8 mL) were added 2-chloro-4-fluoro bromobenzene (34 mg, 0.16 mmol), followed by BINAP (7.5 mg, 0.012 mmol) and Cs_2CO_3 (73 mg, 0.22 mmol) in one portion each. The resulting mixture was degassed twice. Then, $Pd(OAc)_2$ (5 mg, 0.008 mmol) was added in one portion and the mixture was heated to 110 °C for 3 h. The conversion was monitored by TLC. The reaction flask was cooled down to room temperature, and rinsed into a seperatory funnel. It was extracted with ethyl acetate (3x 10 mL), washed with water (1x 10mL), and brine (1x10 mL), dried over Na_2SO_4. It was filtered off and concentrated in vacuo to give the crude product that was purified by RP C-18 column chromatography eluted with 20-60% CH_3CN in water in the presence of 0.1% TFA to afford 6-(2-chloro-4-fluoro-phenylamino)-3-(2,6-dichloro-phenyl)-1-methyl-pyrazolo[1,5-a]pyrimidin-2-one (4 mg) as a yellow solid. ^1H NMR (CD_3OD) δ: 8.62 (d, 1H), 8.43 (d, 1H), 7.50 (d, 2H), 7.38-7.34 (m, 1H), 7.24 (dd, 1H), 7.06-6.96 (m, 2H), 3.79 (s, 3H); LCMS: 439.22 $(M+1)^+$.

EXAMPLE 3



3-Chloro-N-[3-(2,6-dichloro-phenyl)-1-methyl-2-oxo-1,2-dihydro-pyrazolo[1,5-a]pyrimidin-6-yl]-4-fluoro-benzenesulfonamide: To a solution 6-amino-3-(2,6-dichloro-phenyl)-1-methyl-pyrazolo[1,5-a]pyrimidin-2-one (50 mg, 0.16 mmol) from step 5 of Example 1 in DCM (0.8 mL) was added 3-chloro-4-fluoro-benzenesulfonyl chloride (34 mg, 0.18 mmol), followed by pyridine (19.4 mL mg, 0.24 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The conversion was monitored by TLC. The mixture was concentrated down to give the crude product that was purified by silica gel column chromatography eluted with 0-10% MeOH in DCM to afford 3-chloro-N-[3-(2,6-dichloro-phenyl)-1-methyl-2-oxo-1,2-dihydro-pyrazolo[1,5-a]pyrimidin-6-yl]-4-fluoro-benzene sulfonamide (35 mg) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ: 8.60 (d, 1H), 7.95 (d, 1H), 7.93 (dd, 1H), 7.70-7.68 (m, 1H), 7.31-7.23 (m, 3H), 7.18-7.14 (m, 1H), 3.75 (s, 3H); LCMS: 503.08 $(M+1)^+$.

EXAMPLE 4



5-(2-Chloro-4-fluoro-phenylamino)-1-(2,6-dichloro-phenyl)-3-methyl-pyrazolo [1,5a]pyrimidin-2-one:

Step 1

2-Bromo-N-(2,6-dichloro-phenyl)-propionamide: A 250 mL round bottom flask were charged with 2-bromopropanoic acid (50 g, 326.80 mmol) and sulfuryl dichloride (40 mL). The resulting solution was refluxed 3 hours. Then, the excess sulfuryl dichloride was removed on a rotary evaporator. The

resulting residue was transferred into a 3-necked 1 L round bottom flask and dissolved in 400 mL acetic acid. To this mixture was added 2, 6-dichlorobenzenamine (37.5 g, 231.48 mmol). The resulting solution was allowed to stir at room temperature. Upon the completion, the reaction mixture was then quenched by addition of 1 L saturated solution of $NaHCO_3$. The resulting mixture was filtered off and washed with petroleum ether to afford 50 g of 2-bromo-N-(2,6-dichlorophenyl) propionamide in 52 % yield as a white solid. This was used for the next step without further purification. ^1H NMR ($CDCl_3$): δ 7.89 (s, 1H), 7.41 (m, 2H), 7.27 (m, 1H), 4.65 (q, 1H), 2.04 (d, 3H).

Step 2

2-Cyano-N-(2,6-dichloro-phenyl)-2-methyl-acetamide: A 500 mL 3-necked round bottom flask was charged a solution of potassium cyanide (50 g, 230.34 mmol) in H_2O (170 mL) and DMF (200 mL). To this mixture was then added 2-bromo-N-(2,6-dichlorophenyl)propionamide (167 g, 561 mmol). The resulting solution was heated to 60 °C in an oil bath for 4. The reaction was monitored by TLC (EtOAc/PE = 1:1). Upon the completion, it was cooled down to room temperature and was poured into ice water. The resulting precipitate was filtered off and dried in an oven under reduced pressure to afford 134 g of 2-cyano-N-(2,6-dichloro-phenyl)-2-methyl-acetamide as a pale yellow solid in 83% yield. This was used for the next step without further purification.

Step 3

N-(2,6-Dichloro-phenyl)-2-(N-hydroxycarbamimidoyl)-propionamide: A 500 mL 3-necked round bottom flask was charged with 2-cyano-N-(2,6-dichloro-phenyl)-2-methyl-acetamide (12 g, 49.78 mmol) and $NH_2OH.HCl$ (14 mg, 0.20 mmol). To this was added triethylamine (20.2 g, 200.00 mmol) followed by propan-2-ol (250 mL). The resulting solution was allowed to reflux for 3 h. Upon the completion of the reaction monitored by TLC (CH_2Cl_2/MeOH = 10:1), the mixture was cooled down in iced water. The residue was dissolved in 150 mL of H_2O. The resulting solution was extracted with diethyl ether (3 x 300 mL). The combined organic layers were dried over Na_2SO_4, filtered off and concentrated in vacou to afford 9 g of N-(2,6-dichloro-phenyl)-2-(N-hydroxycarbamimidoyl)-propionamide as a yellow solid in 59% yield. This was used for the next step without further purification.

Step 4

N-(2,6-Dichloro-phenyl)-2-(5-methyl-[1,2,4]oxadiazol-3-yl)-propionamide: A 500 mL round bottom flask was charged with (Z)- N-(2,6-dichloro-phenyl)-2-(N-hydroxycarbamimidoyl)-propionamide (20 g, 72.43mmol) and dissolved in acetic acid (200 mL). To this mixture was added Ac_2O (8.60g, 84.24mmol) and allowed to stir at r.t. for 2 h. Then, the resulting solution was heat to reflux for 2 hours. The reaction was monitored by TLC (EtOAc/PE = 1:1). It was cooled dwon to room temperature and concentrated to 1/3 of the actual volume on a rotary evaporator. The residue was then added 200 mL H_2O. The resulting precipitate was filtered off and the cake was washed with water (2 x 40mL) to afford

14 g of N-(2,6-dichloro-phenyl)-2-(5-methyl-[1,2,4]oxadiazol-3-yl)-propionamide as a brown solid. ^{1}H NMR (DMSO) δ: 7.52 (m, 2H), 7.36 (m, 1H), 4.05 (q, 1H), 2.55 (s, 3H), 1.56(d, 3H).

Step 5

N-[1-(2,6-Dichloro-phenyl)-4-methyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl]-acetamide: A 500 mL round bottom flask was charged with a solution of N-(2,6-dichloro-phenyl)-2-(5-methyl-[1,2,4]oxadiazol-3-yl)-propionamide (12 g, 40.00 mmol) in ethanol (340 mL). To the mixture was added KOH (6.7 g, 119.41 mmol). The resulting solution was refluxed for 20 h in an oil bath. The reaction was monitored by TLC (EtOAc/PE = 1:1). The flask was cooled down to r.t. and pH was adjusted to 8 by addition of AcOH. The mixture was then concentrated on a rotary evaporator. The reaction mixture was then quenched with 30 mL ice water. The resulting solution was extracted with EtOAc (2 x 50mL) and the combined organic layers were dried over Na_2SO_4, filtered off and concentrated in vacuo to afford 10 g of N-[1-(2,6-dichloro-phenyl)-4-methyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl]-acet- amide as a yellow solid in 83% yield. This was used without further purification.

Step 6

5-Amino-2-(2,6-dichloro-phenyl)-4-methyl-1,2-dihydro-pyrazol-3-one: A 50 mL 3-necked round bottom flask was charged with a solution of N-(1-(2,6-dichlorophenyl)-4-methyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl)acetamide (12g, 40.1 mmol) in ethanol (120 mL). Then, it was filled with HCl atmosphere. The resulting solution was refluxed for 3 h in an oil bath. The reaction was monitored by TLC (EtOAc/PE = 1:1). The mixture was cooled down to r.t. and concentrated in vacuo. The reaction mixture was then added 15 mL H_2O and pH was adjusted to 6 by addition of 30% aqueous NH_4OH. The resulting mixture was then extracted with EtOAc (4 x 40 mL) and the combined organic layers were dried over Na_2SO_4. Filtered off and concentrated in vacuo to afford 10g of 5-amino-2-(2,6-dichloro-phenyl)-4-methyl-1,2-dihydro-pyrazol-3-one as a light yellow solid in 97% yield.

Step 7

N-[1-(2,6-Dichloro-phenyl)-4-methyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl]-3-ethoxy-acrylamide: A 100 mL round bottom flask was charged with a solution of 5-amino-2-(2,6-dichloro-phenyl)-4-methyl-1,2-dihydro-pyrazol-3-one (3 g, 11.63 mmol) in DMF (70 mL). To this was added (E)-3-ethoxyacrylic acid (1.5 g, 12.93 mmol, prepared as described in *Can. J. Chem.* **1985**, *63(10)*, 2787-2797 J. J. L. Hronowski et. al) followed by addition of HOBT (480mg, 3.17mmol) and TBTU (4.2g, 13.13mmol). To the mixture was added DIPEA (7.2 ml). The resulting solution was allowed to stir at 0 °C for 2 h followed by at room temperature for 2 h. The reaction was monitored by TLC (EtOAc/PE = 1:1). The reaction mixture was then quenched by addition of 70 mL H_2O. The resulting solution was extracted with CH_2Cl_2 (4 x 40 mL), filtered off and dried over Na_2SO_4. The filtrate was concentrated in vacuo to afford 5.5 g of crude (E)-N-(1-(2, 6-dichlorophenyl)-4-methyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl)-3-ethoxyacrylamide as a yellow liquid. This was used without further purification.

Step 8

1-(2,6-Dichloro-phenyl)-5-hydroxy-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one: A 250 mL round bottom flask was charged with (E)-N-(1-(2,6-dichlorophenyl)-4-methyl -5-oxo-2,5-dihydro-1H-pyrazol-3-yl)-3-ethoxyacrylamide (5 g, 14.04 mmol) and conc.HCl/C_2H_5OH (10/50 mL). The resulting solution was refluxed for 2 h in an oil bath. The reaction was monitored by TLC (EtOAc/PE = 1:1). The flask was cooled down to room temperature and pH was adjusted to 7 by addition of 30% aqueous solution of $NaHCO_3$. The resulting mixture was rinsed into a seperatory funnel and extracted with EtOAc (4 x 50 mL), dried over Na_2SO_4. Filtered off and concentrated in vacuo to give the crude that was purified on a silica gel column eluted with a 1:10 mixture of EtOAc/PE to afford 1 g of 1-(2,6-dichlorophenyl)-5-hydroxy-3-methylpyrazolo[1,5-a]pyrimidin-2-one in 23% yield as a yellow solid.

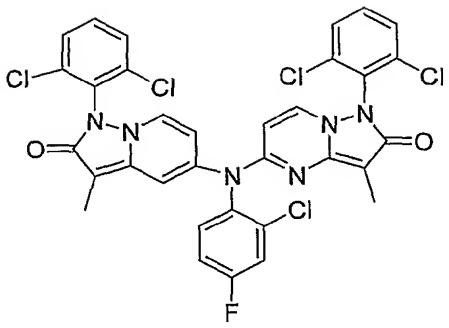
Step 9

5-Chloro-1-(2,6-dichloro-phenyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one: A 50 mL round bottom flask was charged with 1-(2,6-Dichloro-phenyl)-5-hydroxy-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one (500 mg, 1.62 mmol) and $POCl_3$ (5 mL). The resulting solution was allowed to reflux in an oil bath for 2 h. The reaction was monitored by TLC (EtOAc/PE = 1:1). The flask was cooled down to room temperature and the content was concentrated on rotary evaporator. The residue was then added 10 mL of saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dired over Na_2SO_4. Filtered off and concentrated in vacuo to afford 0.36 g of 5-chloro-1-(2,6-dichloro-phenyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one in 68% yield as a yellow solid. This was used for the next step without further purification. ^{1}H NMR ($CDCl_3$) δ: 7.60 (m, 2H), 7.52 (m, 1H), 7.28 (d, 1H), 6.26 (d, 1H), 2.14 (s, 3H).

Step 10

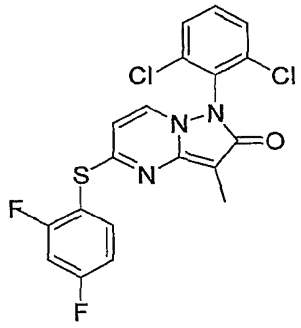
5-(2-Chloro-4-fluoro-phenylamino)-1-(2,6-dichloro-phenyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one: To a solution 5-chloro-1-(2,6-dichloro-phenyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one (100 mg, 0.30 mmol) in toluene (1.6 mL) were added 2-chloro-4-fluoro-phenylamine (44 mg, 0.30 mmol), followed by BINAP (14 mg, 0.022 mmol) and Cs_2CO_3 (132 mg, 0.21 mmol) in one portion each. The resulting mixture was degassed twice. Then, $Pd(OAc)_2$ (10 mg, 0.015 mmol) was added in one portion and the mixture was heated to 110 °C for 3 h. The conversion was monitored by TLC. The reaction flask was cooled down to room temperature, and rinsed into a seperatory funnel. It was extracted with ethyl acetate (3x 25 mL), washed with water (1x 25mL), and brine (1x25 mL), dried over Na_2SO_4. It was filtered off and concentrated in vacuo to give the crude product that was purified by RP C-18 column chromatography eluted with 20-60% CH_3CN in water to 5-(2-chloro-4-fluoro-phenylamino)-1-(2,6-dichloro-phenyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one (22 mg) in 17 % yield as a yellow solid. ^{1}H NMR (CD_3OD) δ: 8.02-7.98 (m, 1H), 7.69-7.60 (m, 4H), 7.35-7.33 (m, 1H), 7.19-7.14 (m, 1H), 6.18 (d, 1H), 1.91 (s, 3H); LCMS: 439.20 $(M+1)^+$.

EXAMPLE 5



5-{(2-Chloro-4-fluoro-phenyl)-[1-(2,6-dichloro-phenyl)-3-methyl-2-oxo-1,2-dihydro-pyrazolo[1,5-a]pyridin-5-yl]-amino}-1-(2,6-dichloro-phenyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one: In an attempt to prepare 5-(2-chloro-4-fluoro-phenylamino)-1-(2,6-dichloro-phenyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one (Example 4), 5-{(2-chloro-4-fluoro-phenyl)-[1-(2,6-dichloro-phenyl)-3-methyl-2-oxo-1,2-dihydro-pyrazolo[1,5-a]pyridin-5-yl]-amino}-1-(2,6-dichloro-phenyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one (12 mg) was isolated as a by product under the same reaction condition in 5 % yield. ^{1}H NMR (CD_3OD) δ: 7.94 (d, 2H), 7.73-7.64 (m, 6H), 7.60-7.52 (m, 2H), 7.35-7.30 (m, 1H), 6.66 (d, 2H), 1.89 (s, 6H); LCMS: 730.26 $(M+1)^+$

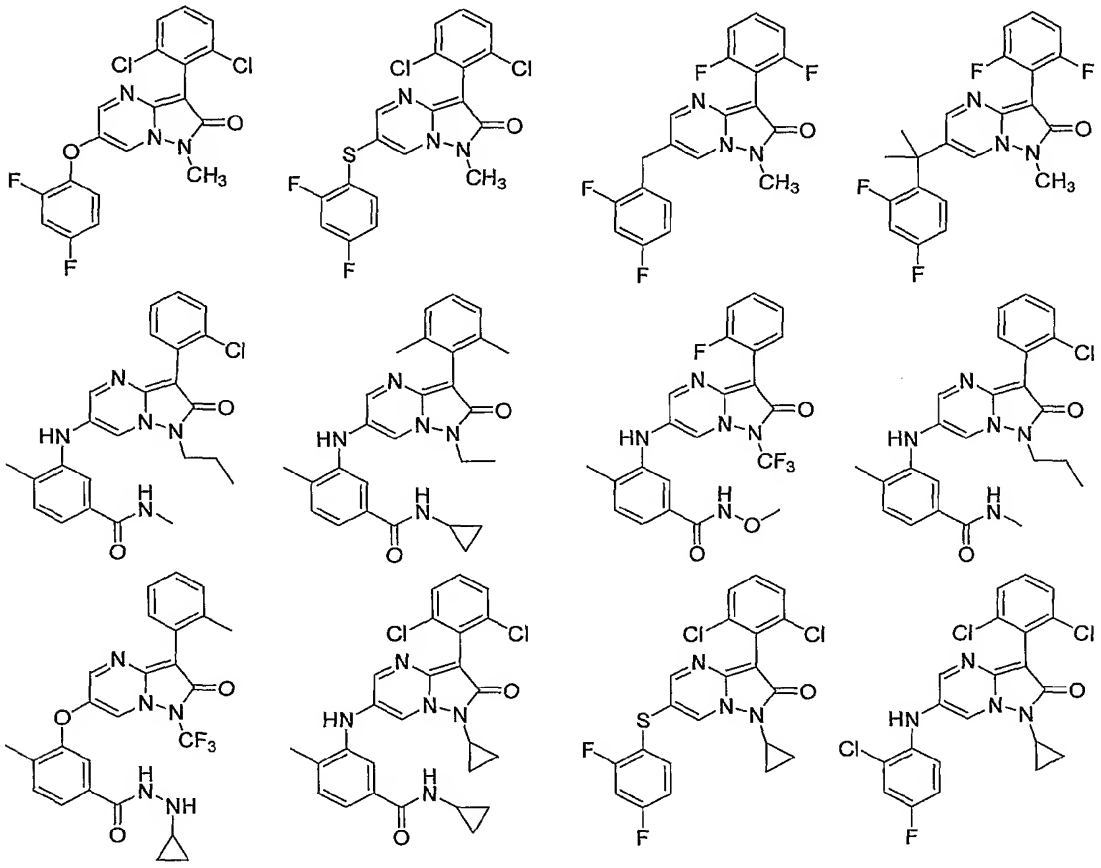
EXAMPLE 6

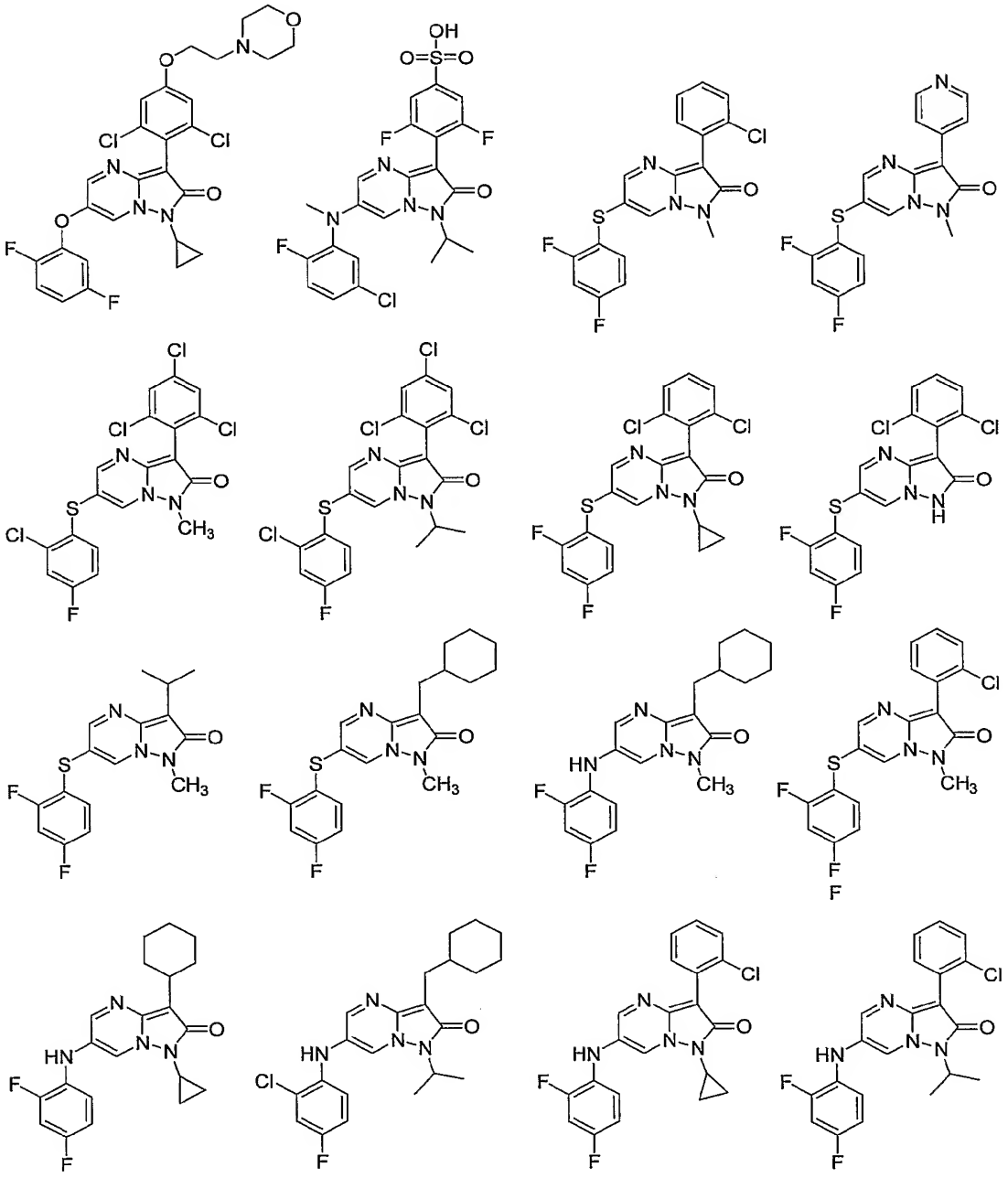


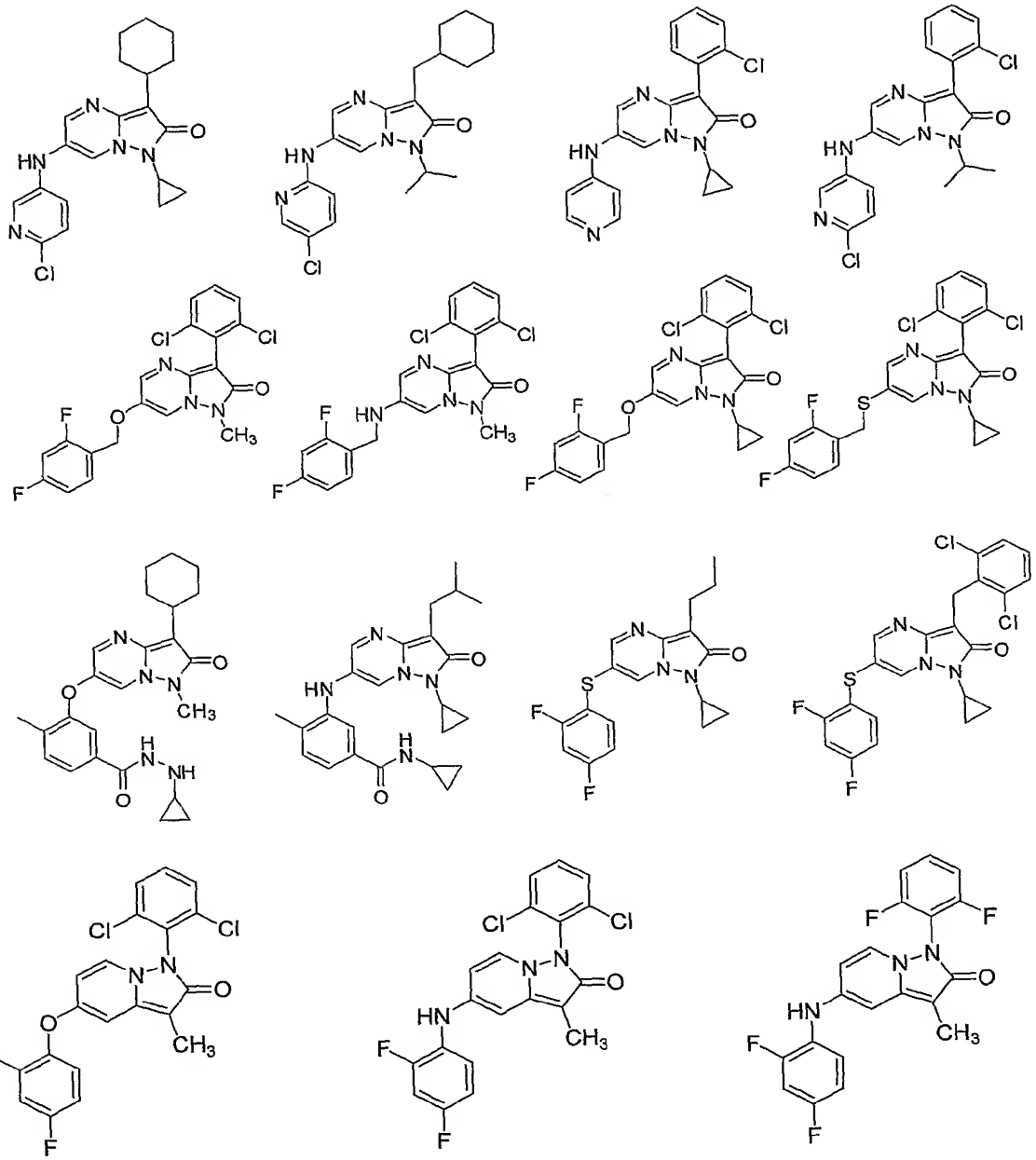
1-(2,6-Difluoro-phenyl)-5-(2,4-difluoro-phenylsulfanyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one: To a solution 5-chloro-1-(2,6-dichloro-phenyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one (25 mg, 0.076 mmol) from step 9 of Example 4 in NMP (1.5 mL) were added 2,4-difluorothiophenol (11 mg, 0.076 mmol), followed by Cs_2CO_3 (25 mg, 0.076 mmol) in one portion each. The resulting mixture was irradiated in a microwave 180 °C for 5 min. The conversion was monitored by TLC. The microwave vessel was cooled down to room temperature, and rinsed into a seperatory funnel. It was extracted with ethyl acetate (3x 10 mL), washed with water (1x 25mL), and brine (1x25 mL), dried over Na_2SO_4. It was filtered off and concentrated in vacuo to give the crude product that was purified by RP C-18 column chromatography eluted with 20-60% CH_3CN in water to afford 1-(2,6-dichloro-phenyl)-5-(2,4-

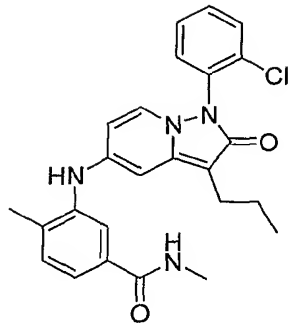
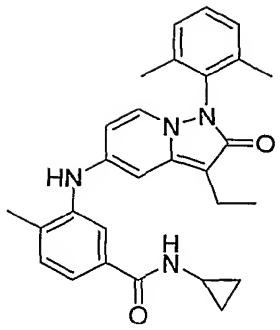
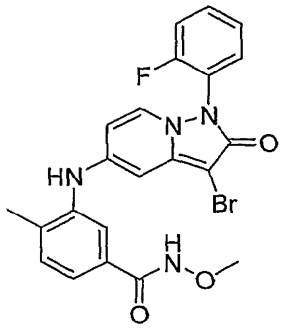
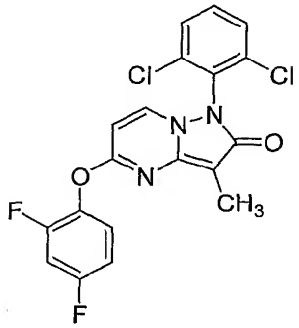
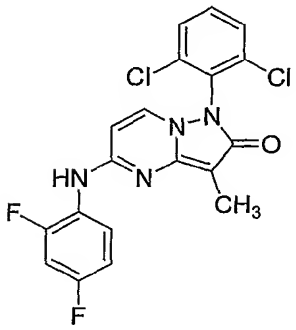
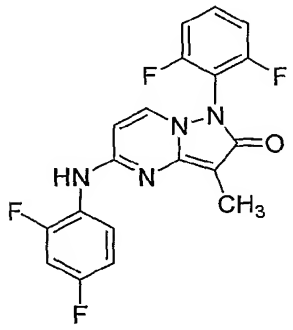
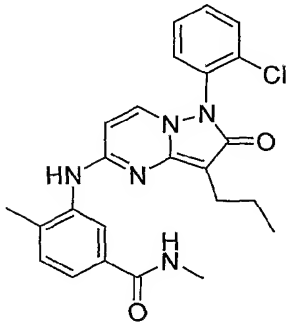
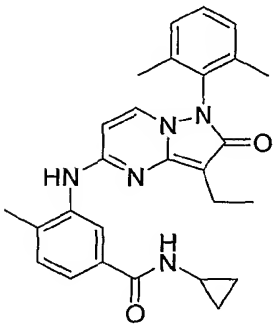
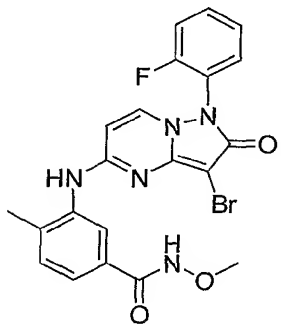
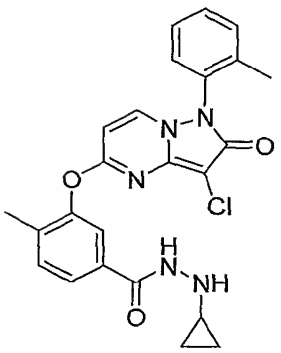
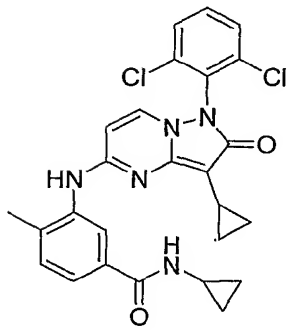
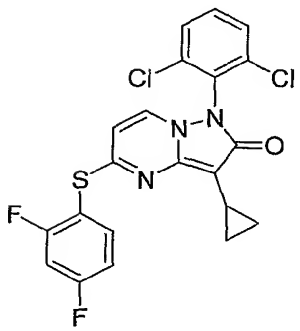
difluoro-phenylsulfanyl)-3-methyl-pyrazolo[1,5-a]pyrimidin-2-one (6 mg) as a yellow solid. ^{1}H NMR (CD_3OD) δ: 7.81-7.80 (d, 1H), 7.75-7.64 (m, 4H), 7.26-7.13 (m, 2H), 6.35-6.32 (d, 1H), 1.87 (s, 3H); LCMS: 440.09 $(M+1)^+$.

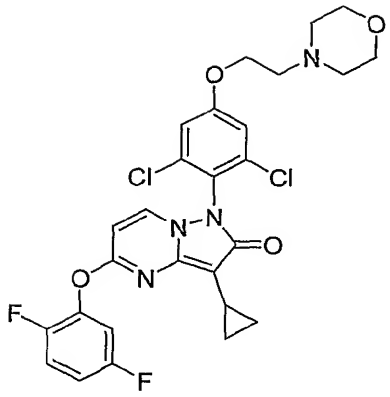
The following compounds can generally be made using methods well known in the art. It is expected that these compounds when made will have activity similar to those that have been made in the examples above.

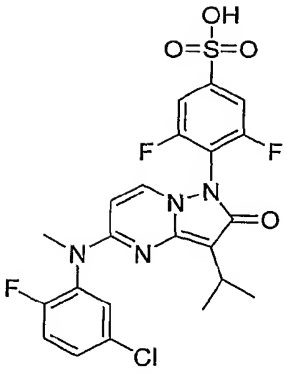


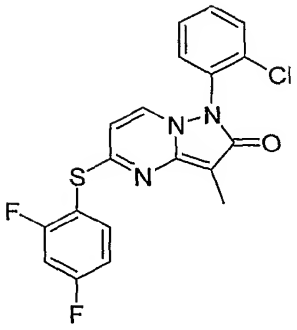


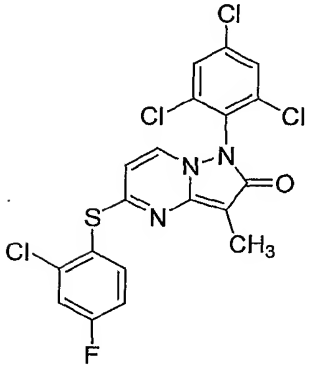


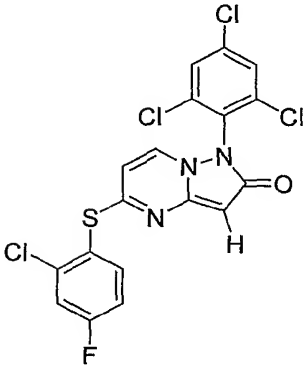













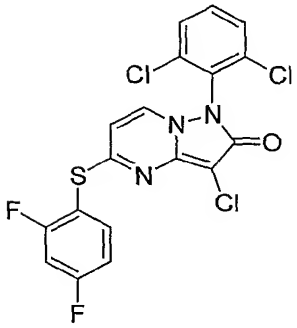


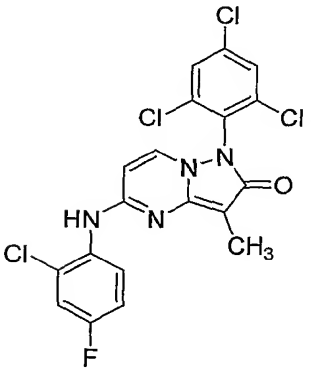


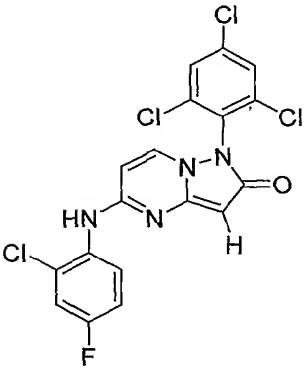


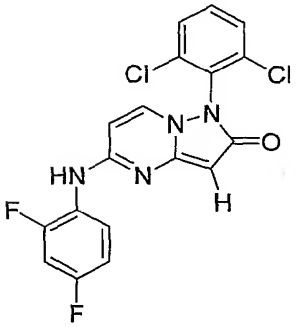


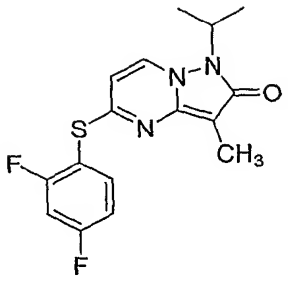
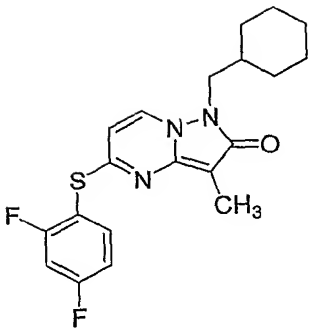
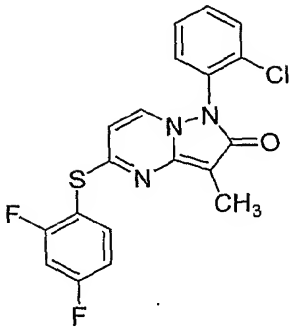
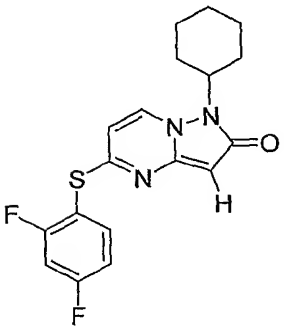
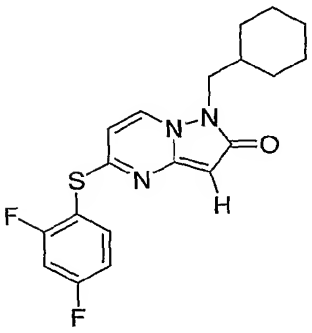
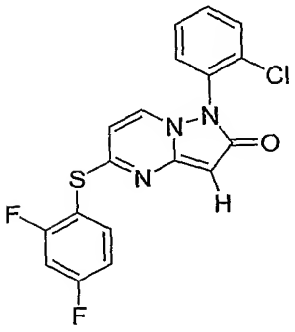
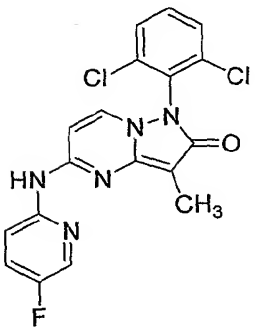
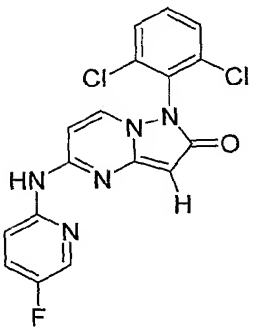
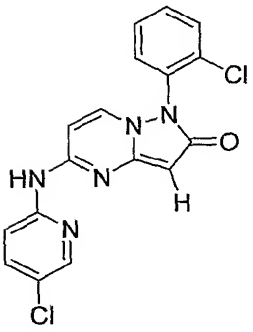
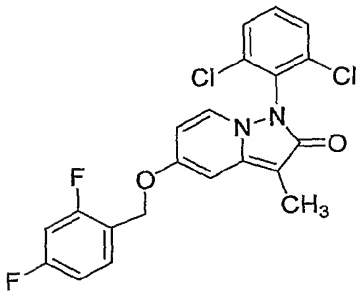
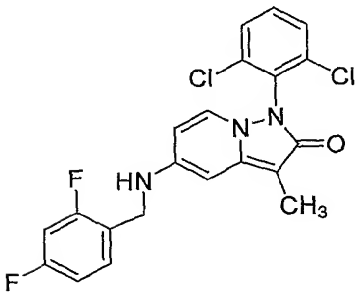
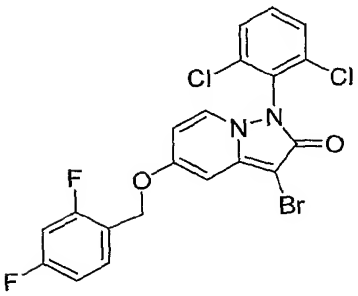


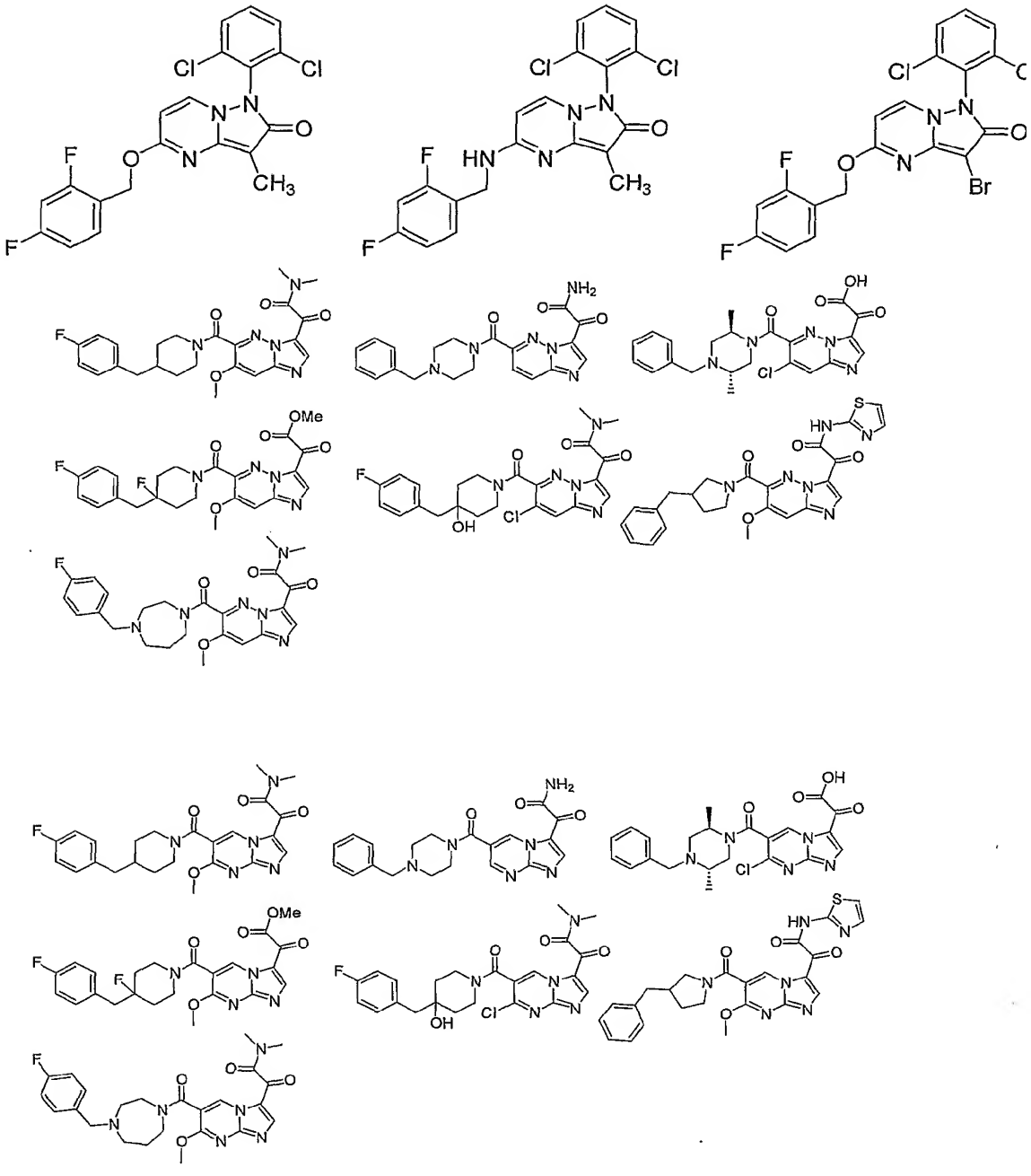


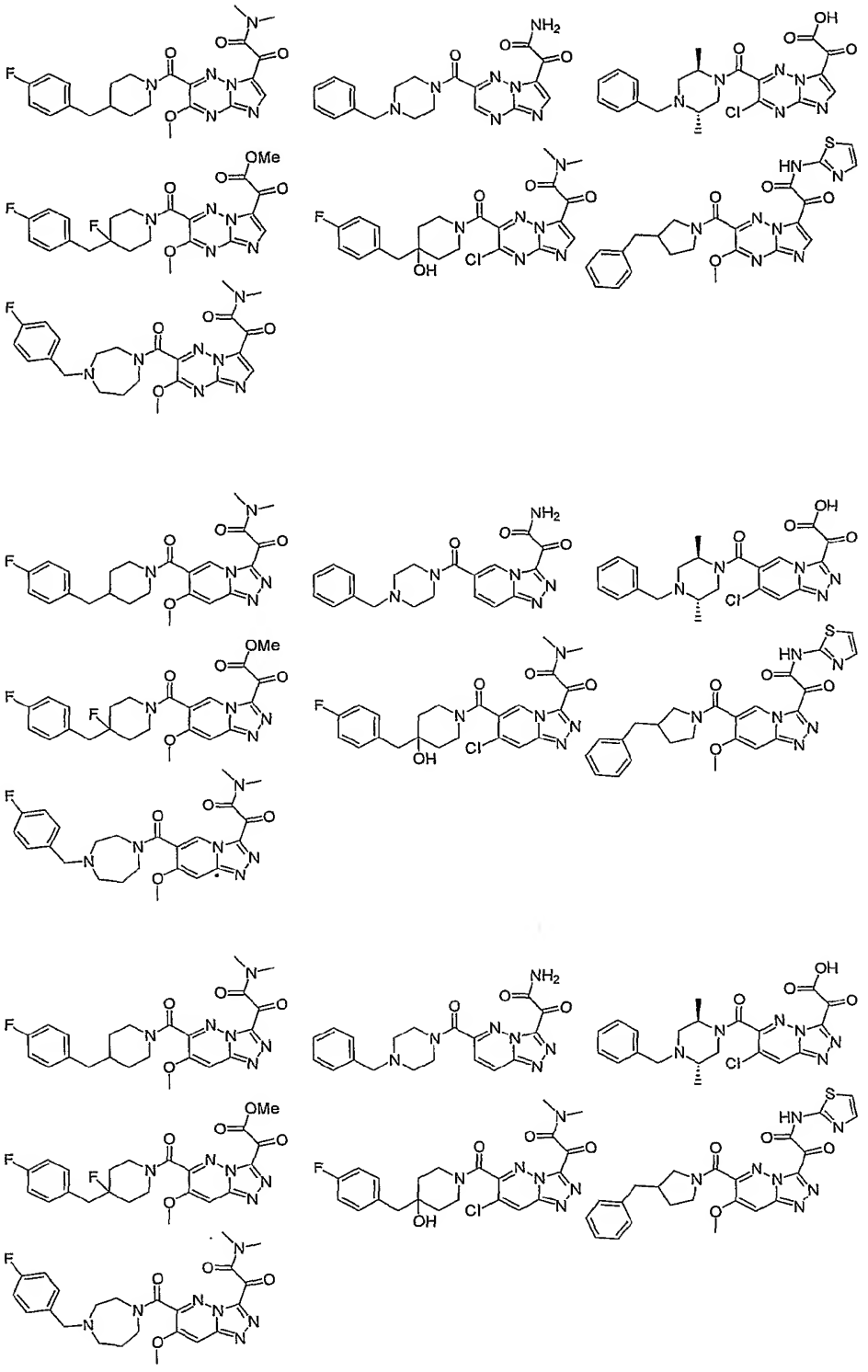


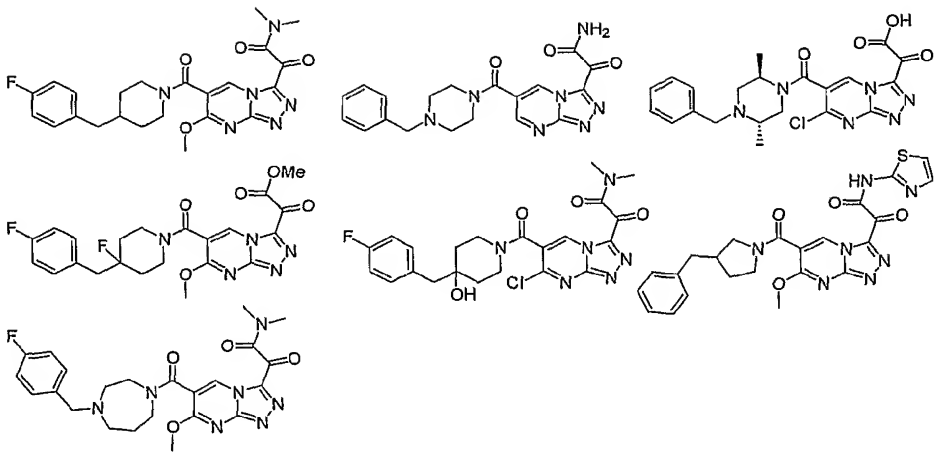


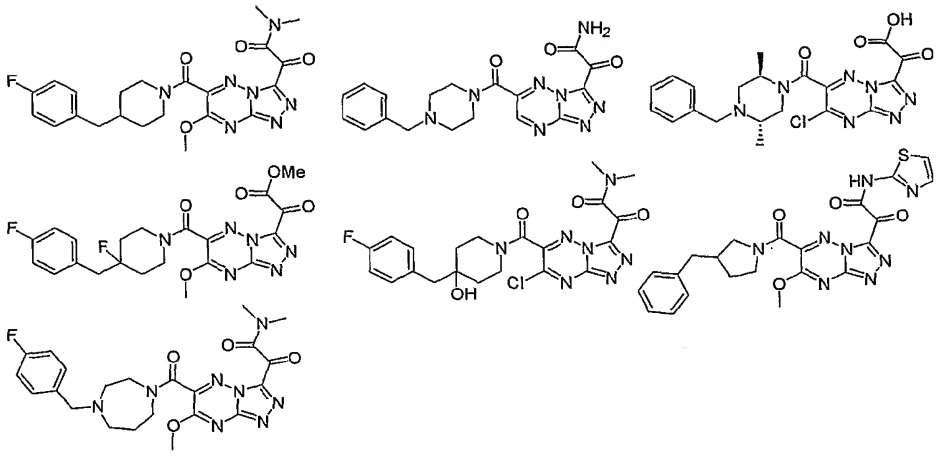


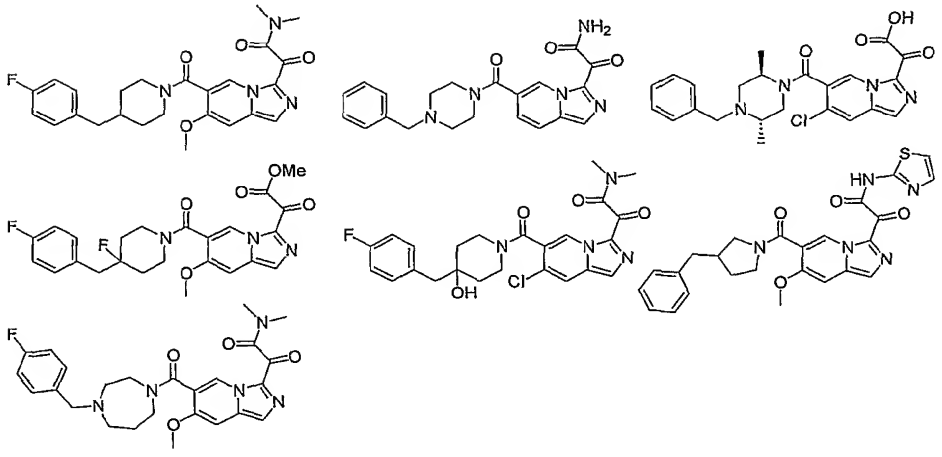













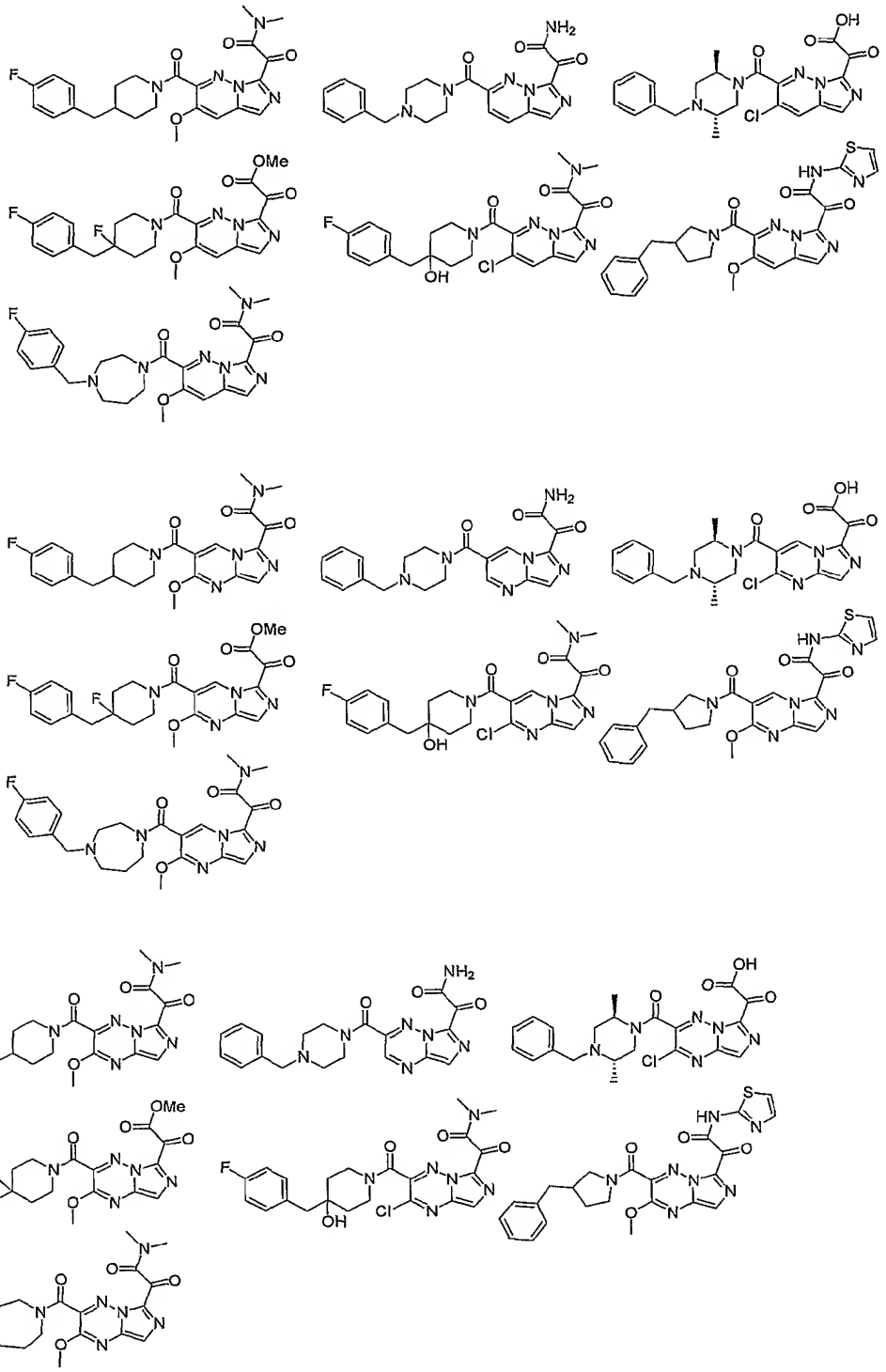


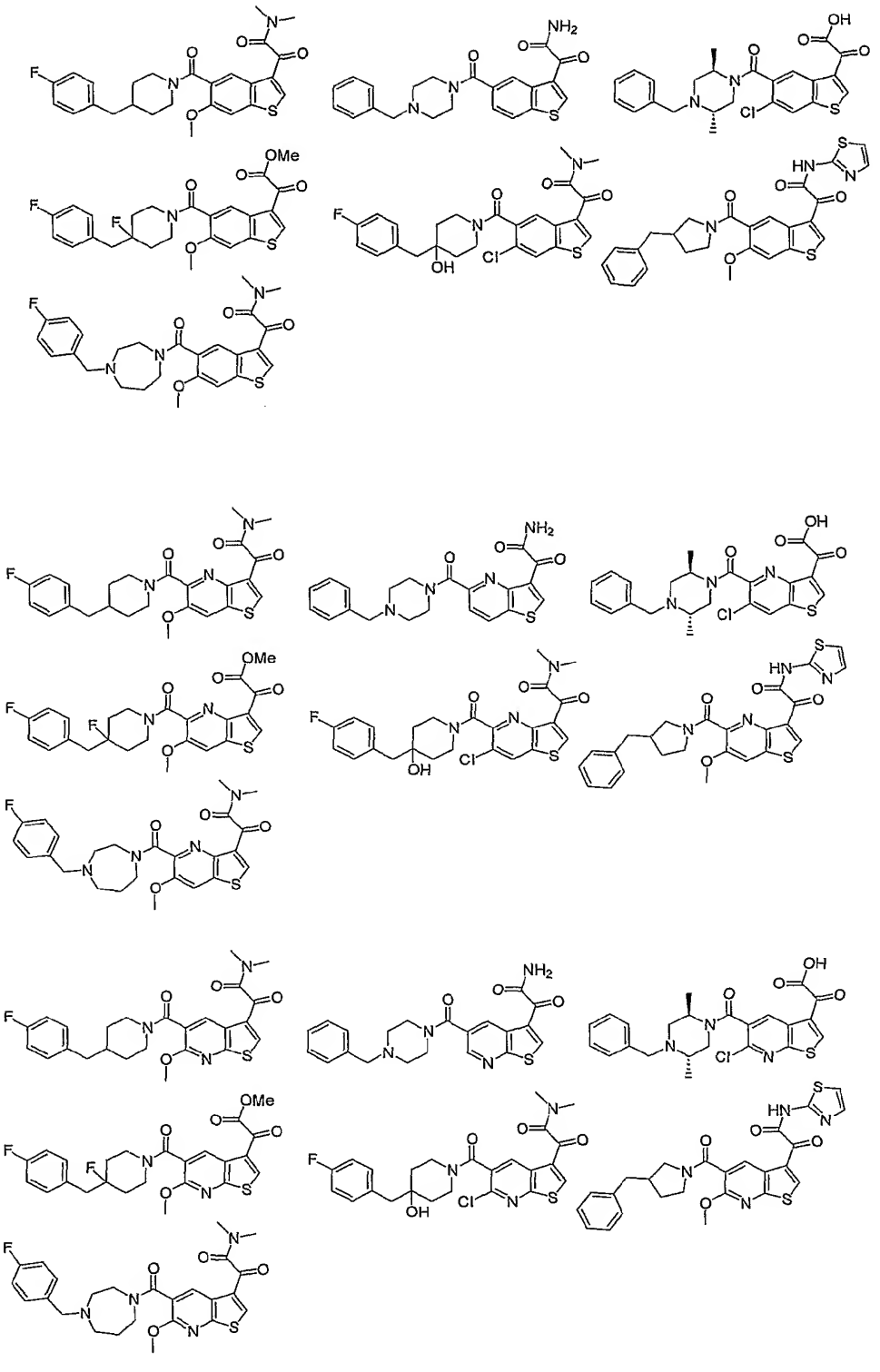


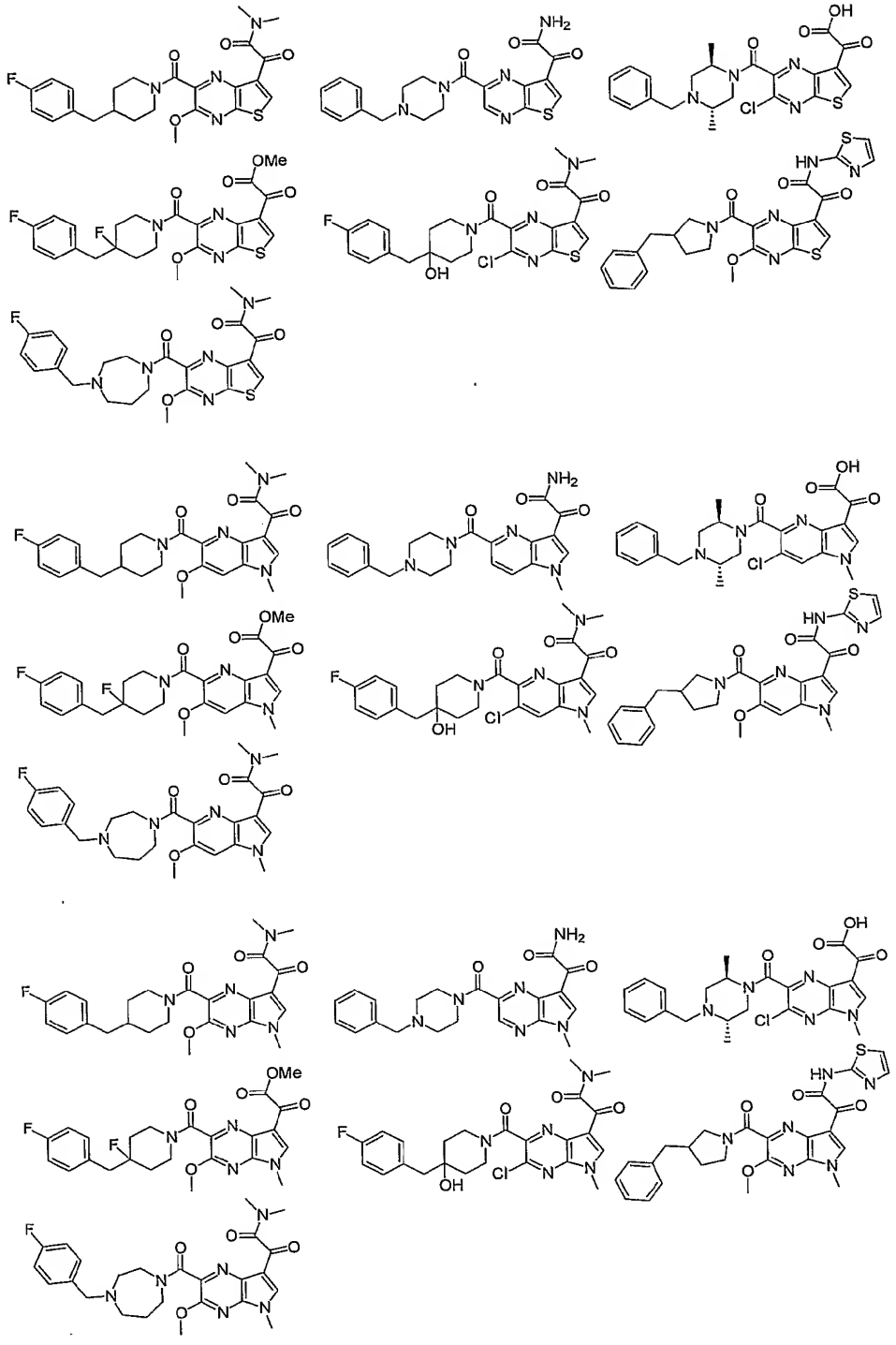


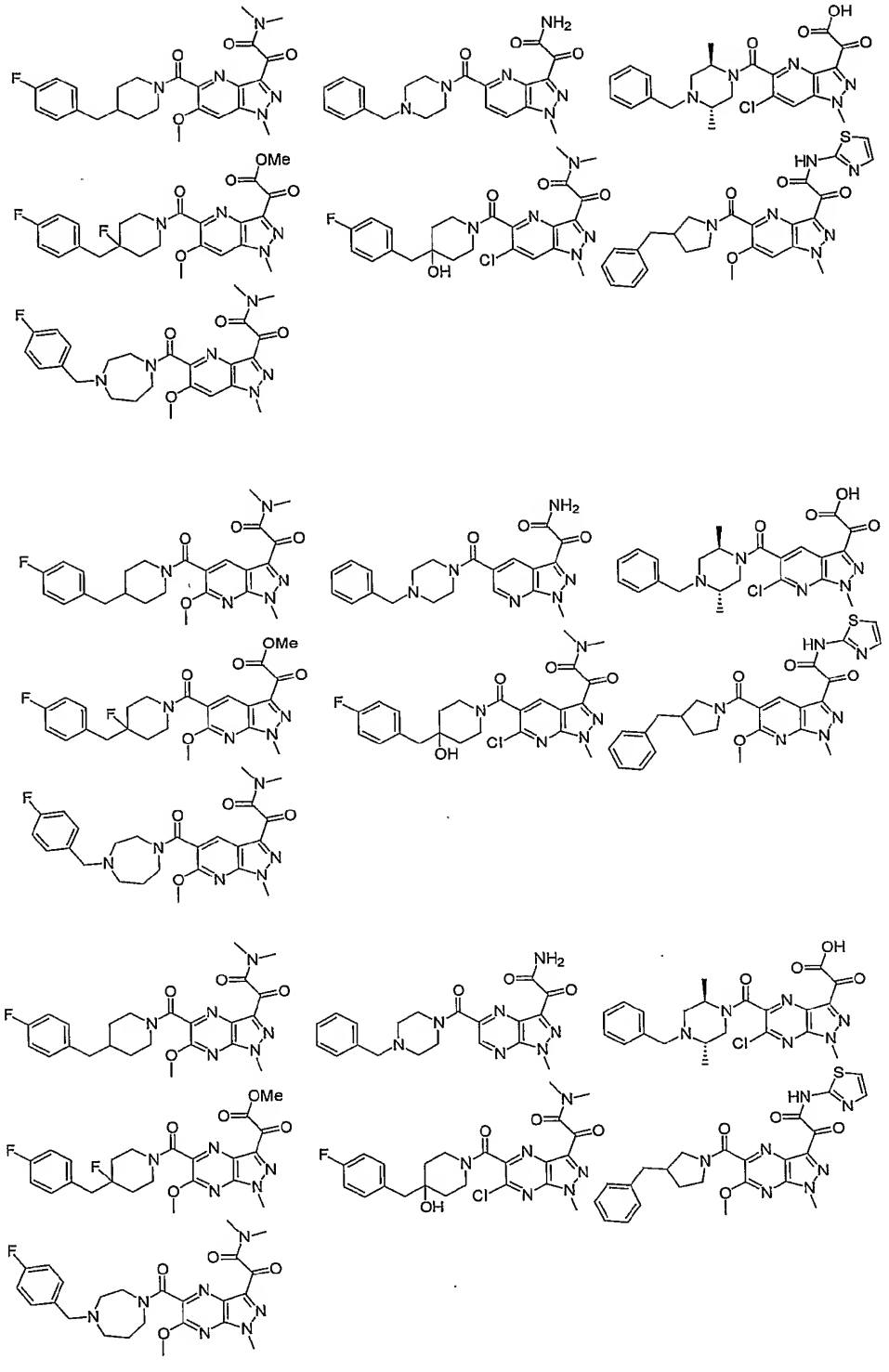


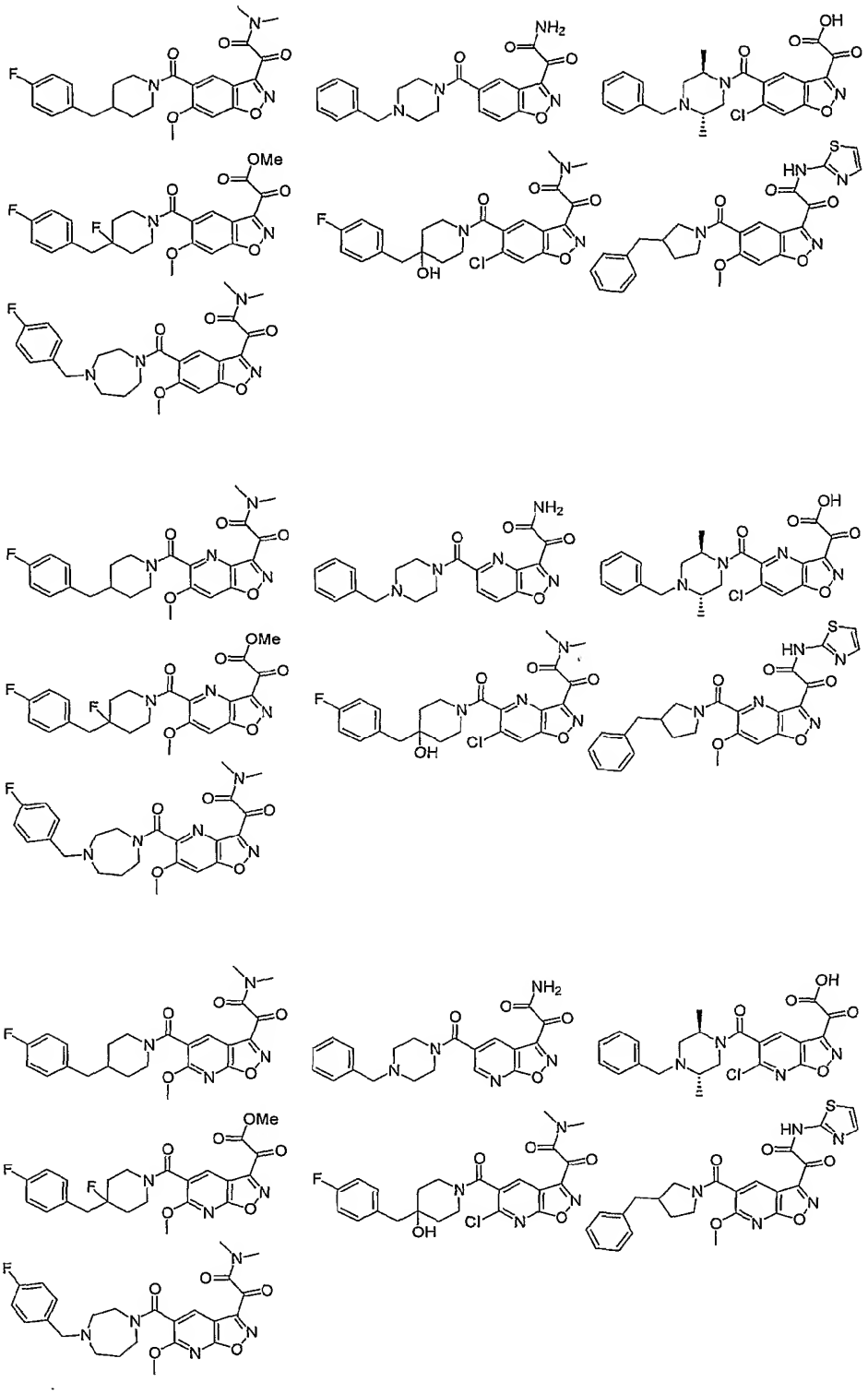


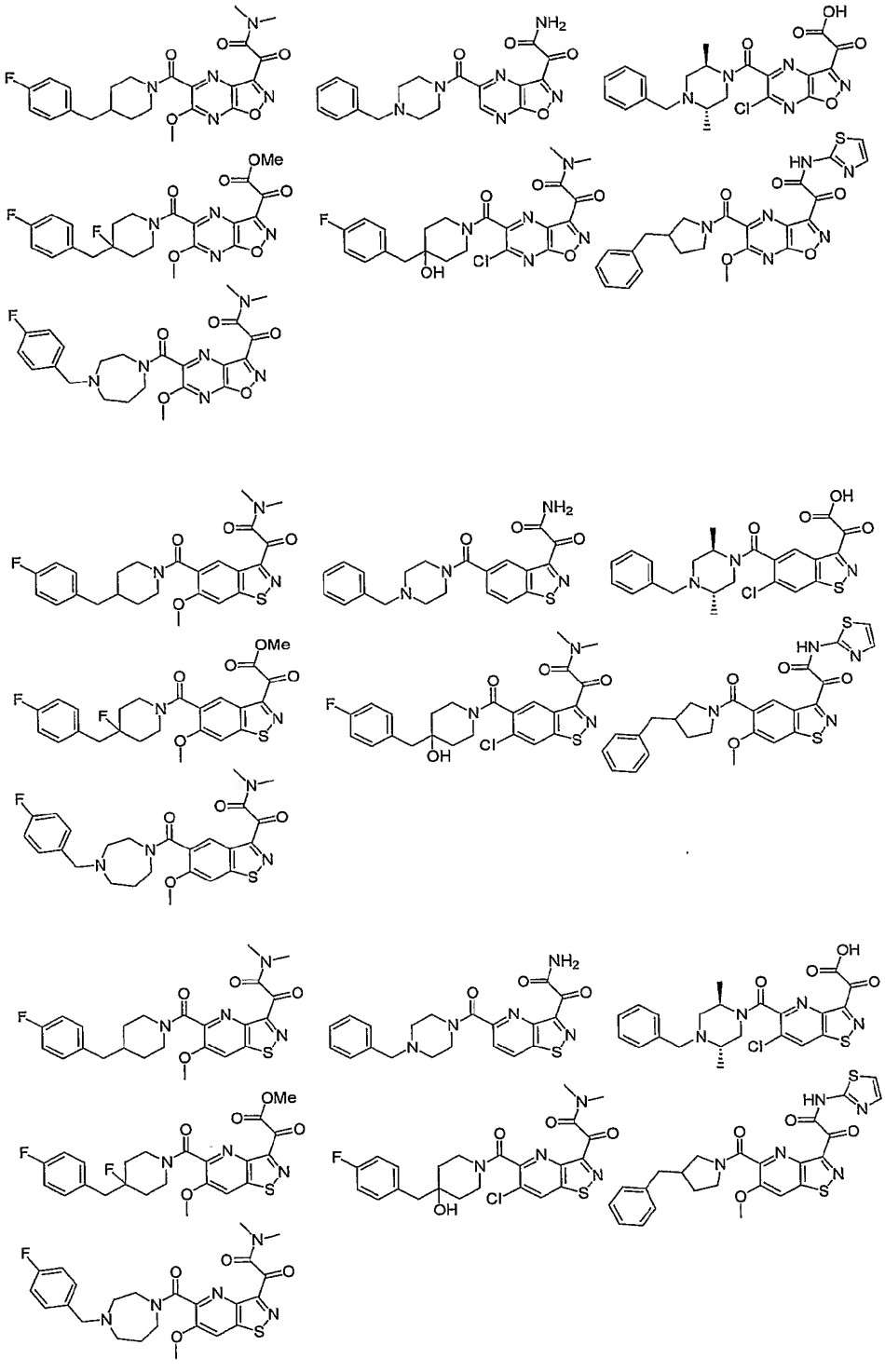


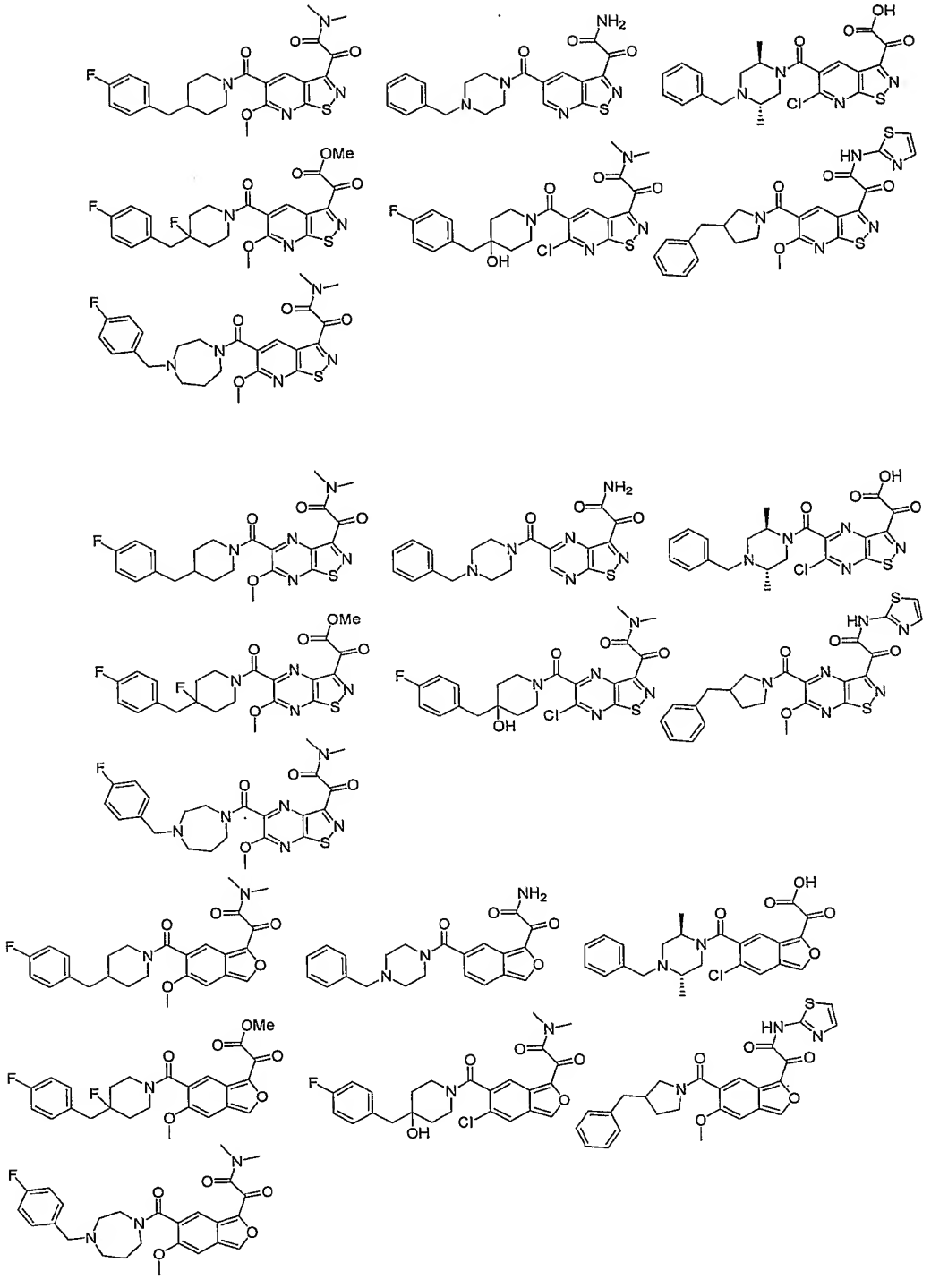


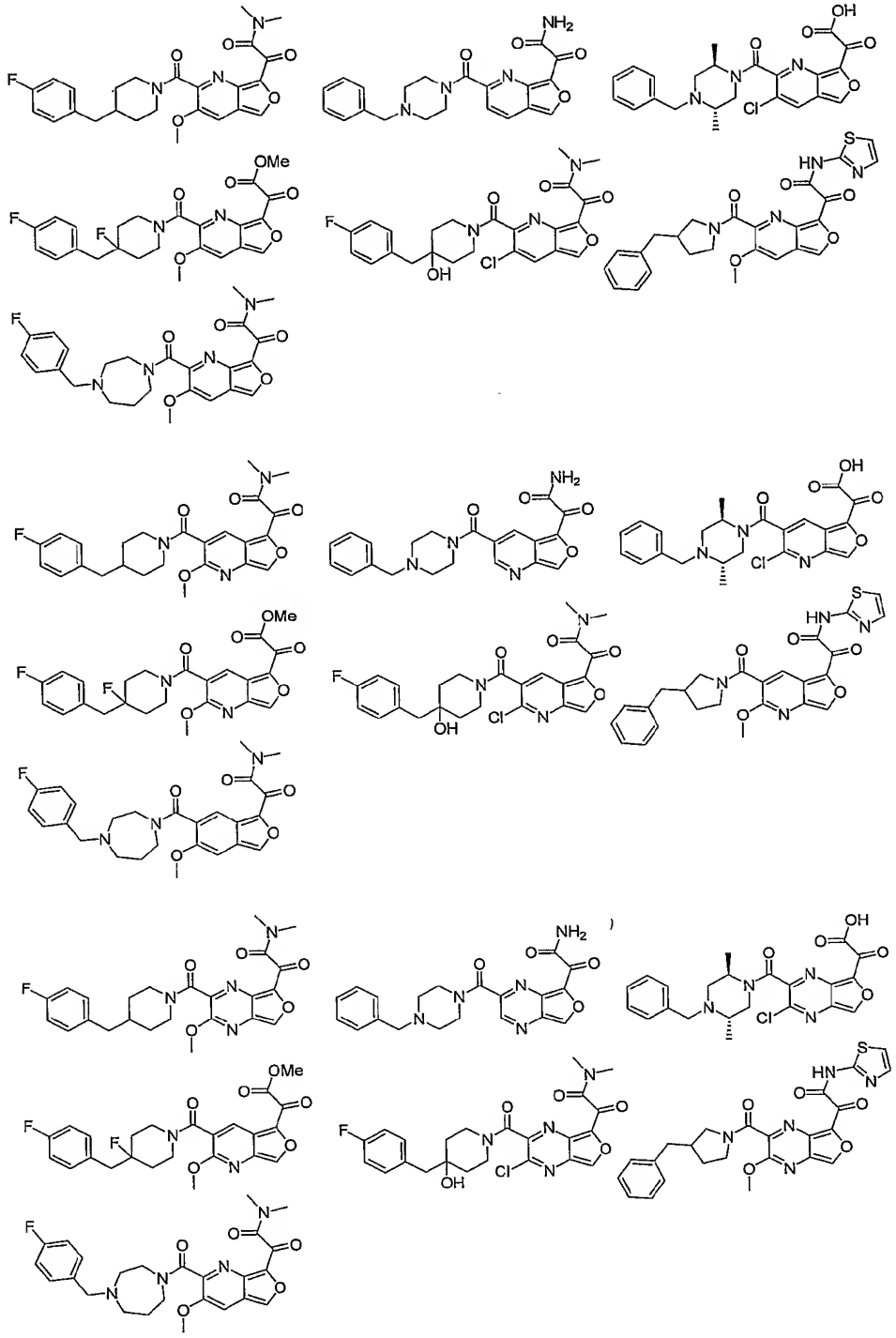


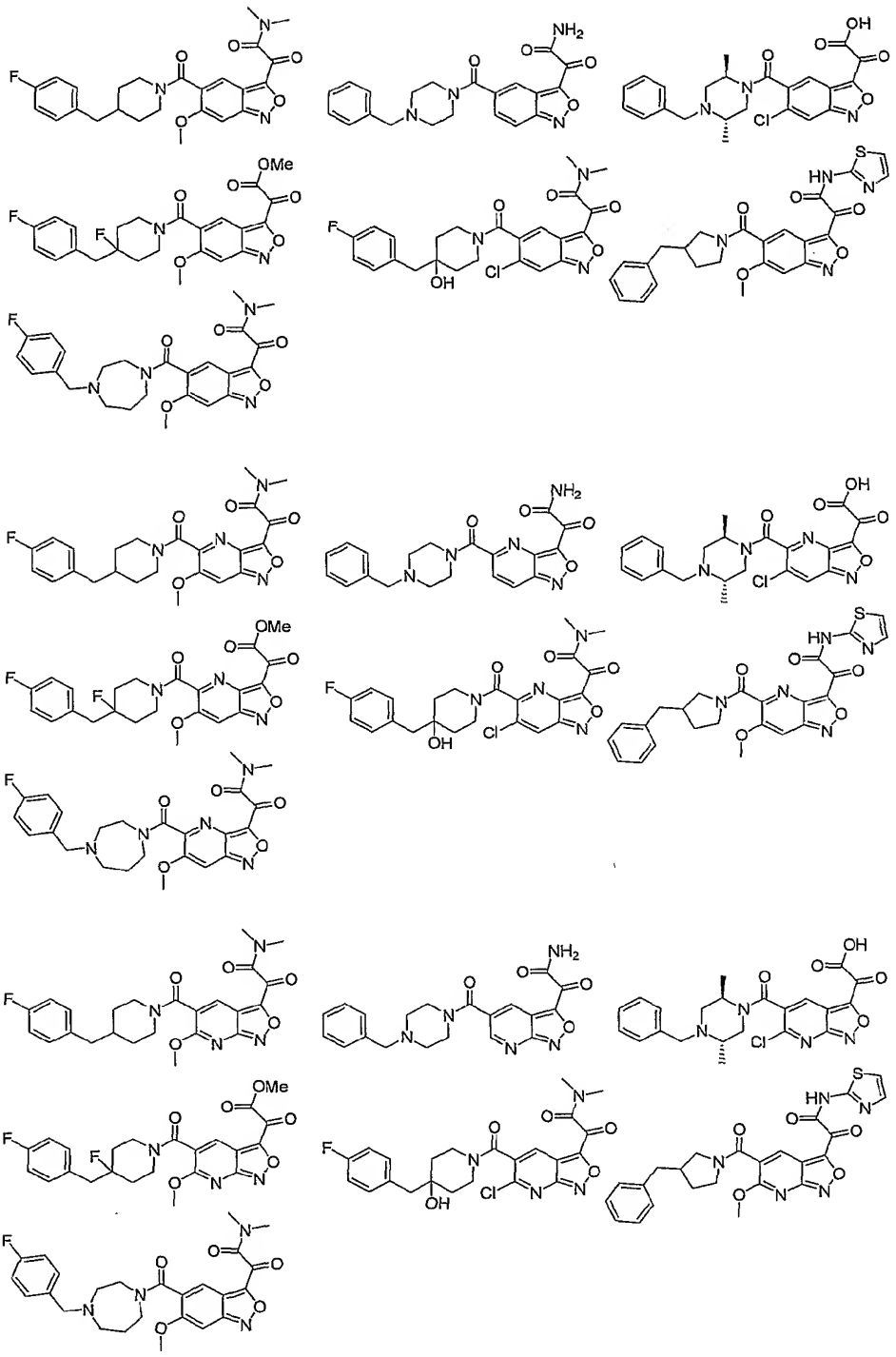


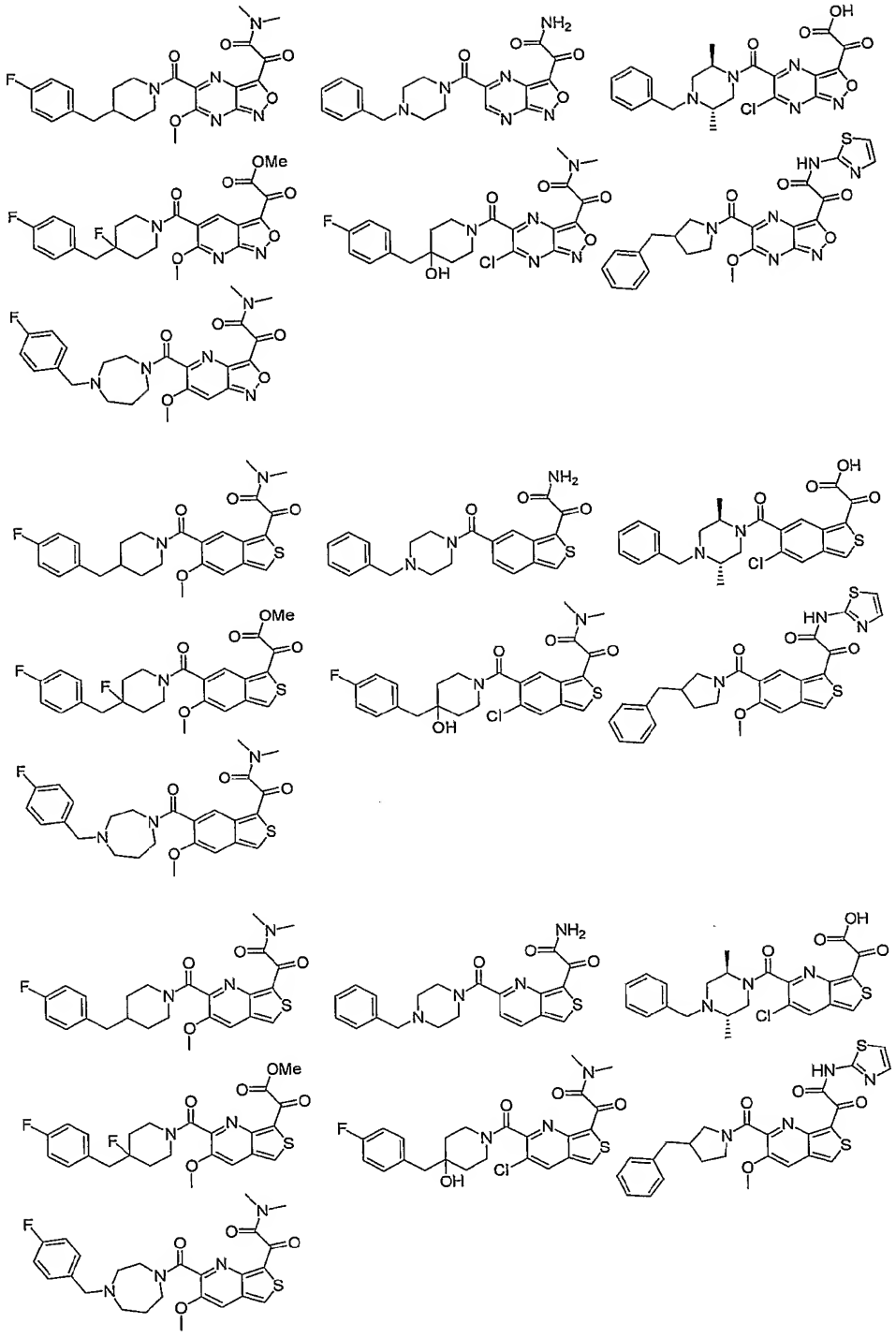


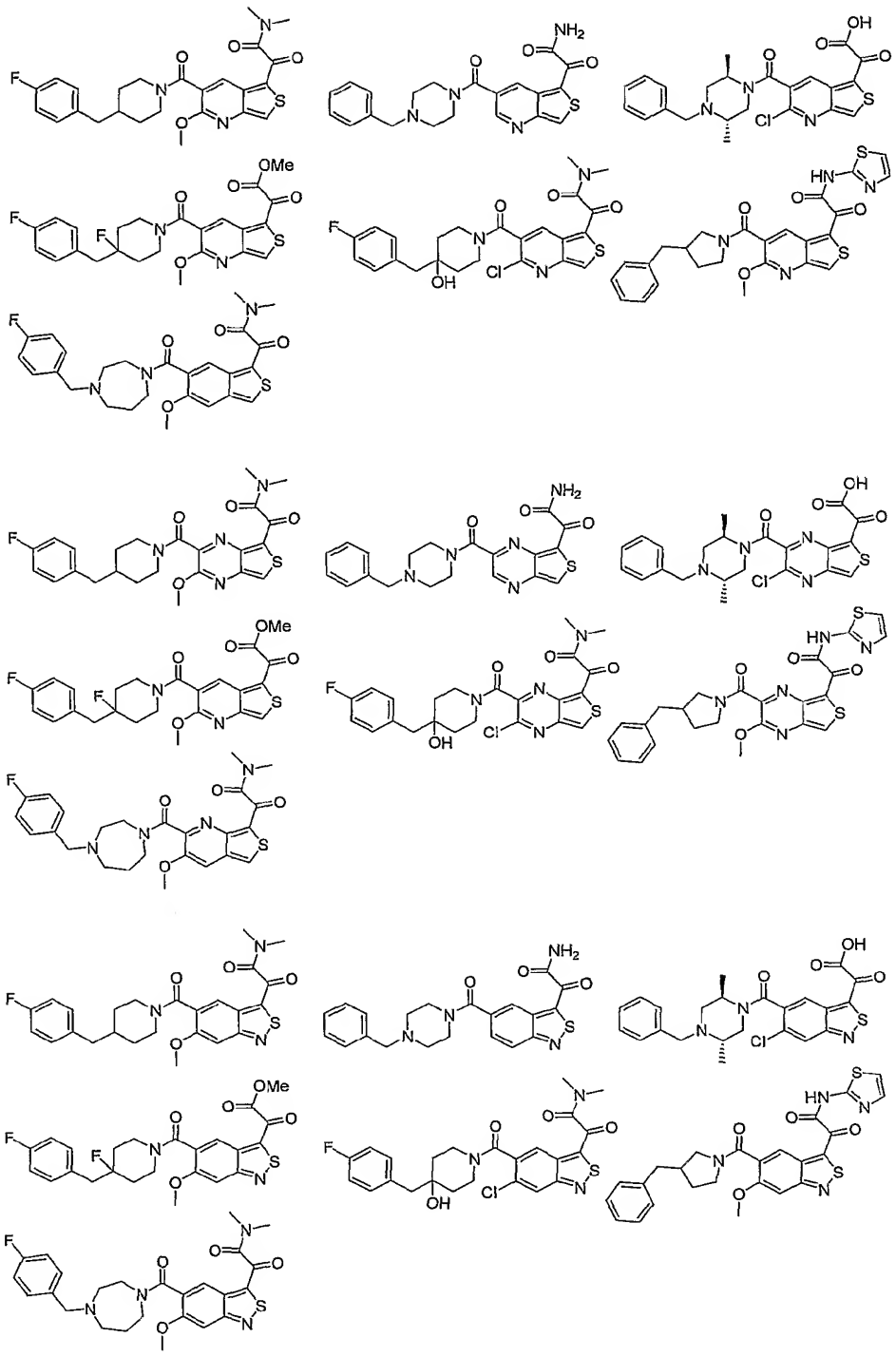


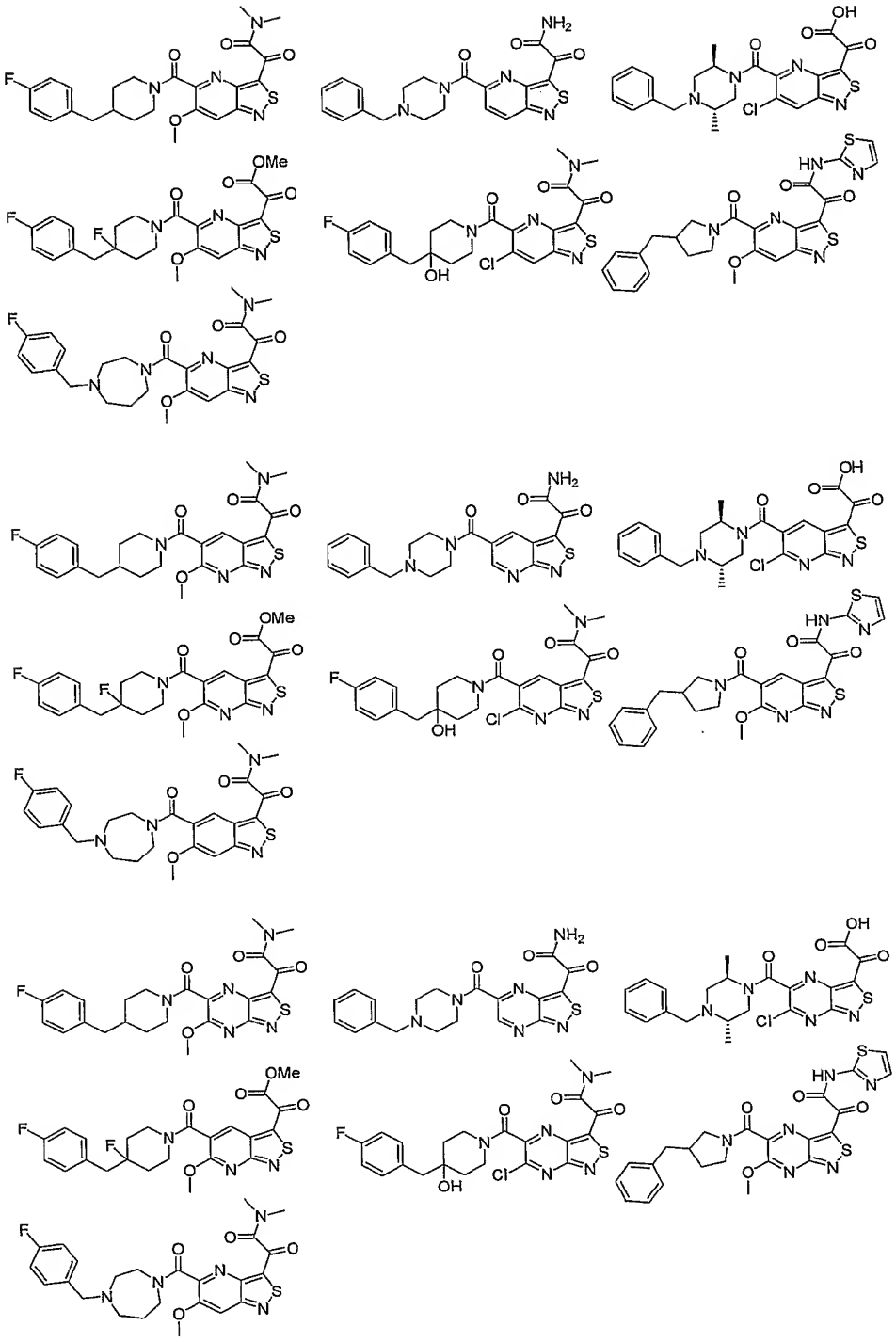


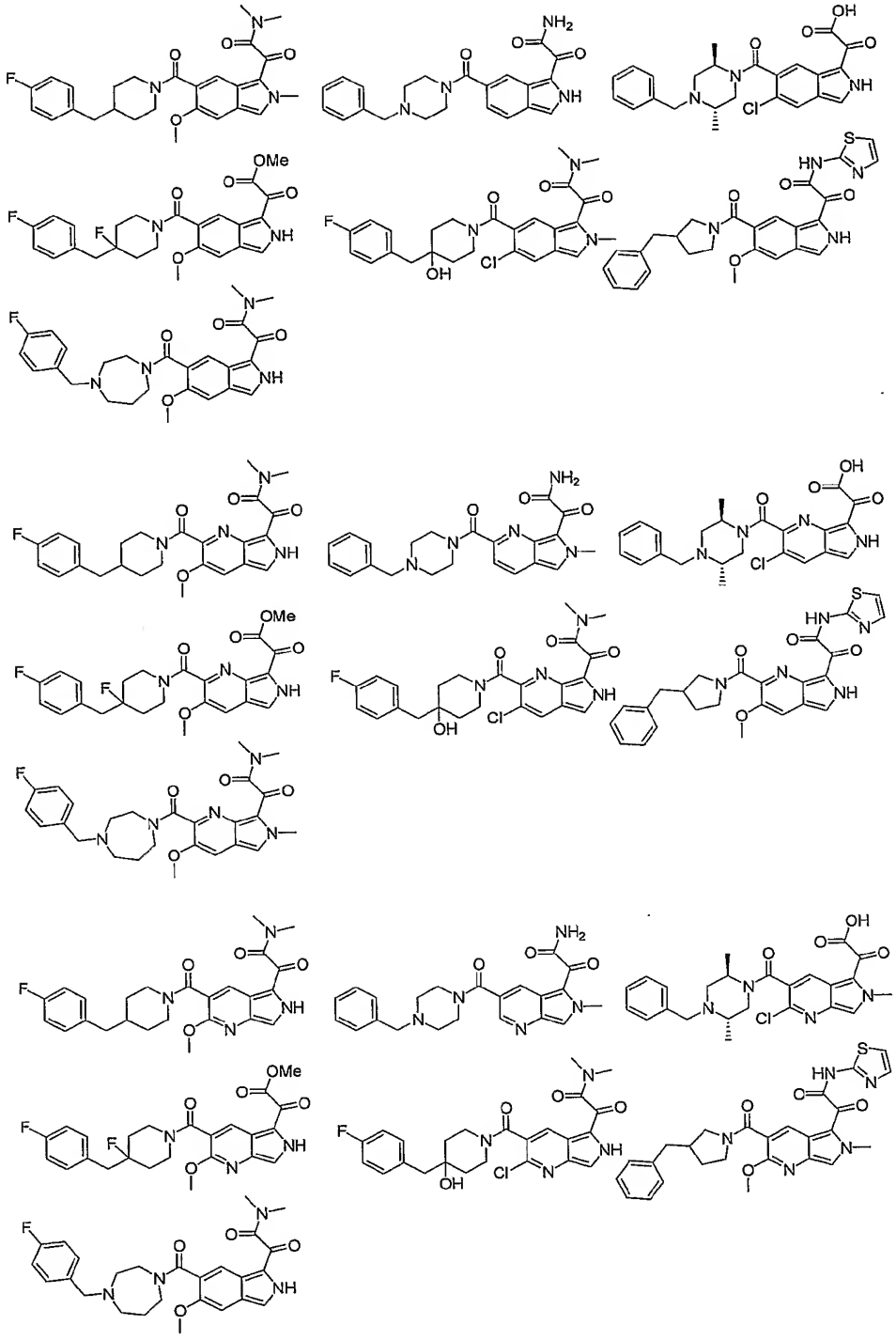


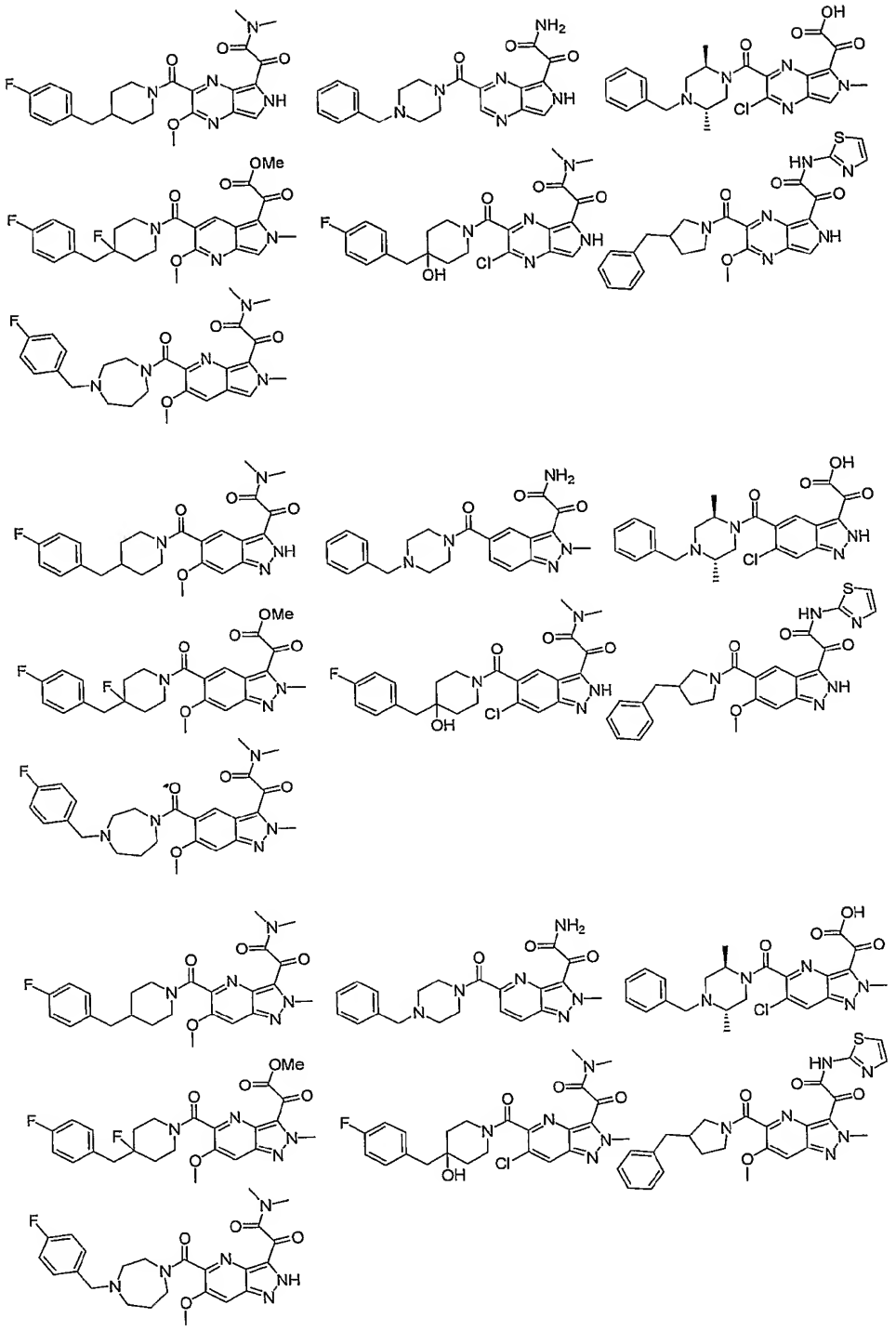


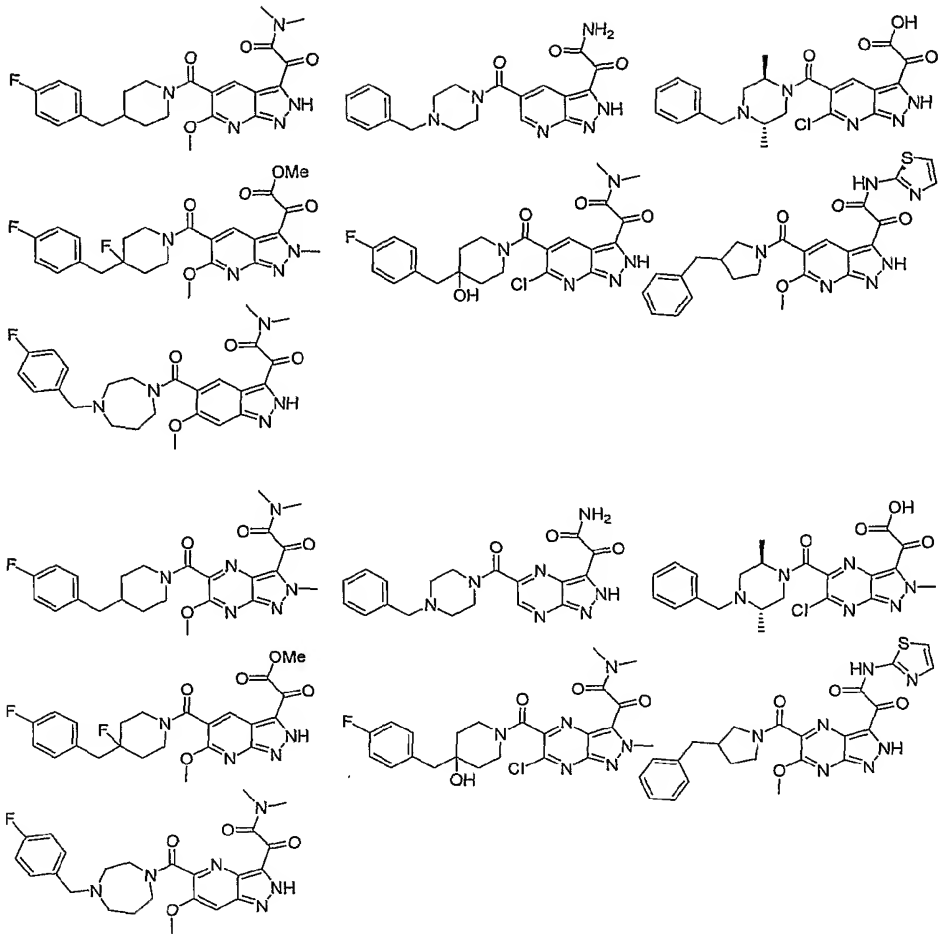












The following compounds are represented herein using the Simplified Molecular Input Line Entry System, or SMILES. SMILES is a modern chemical notation system, developed by David Weininger and Daylight Chemical Information Systems, Inc., that is built into all major commercial chemical structure drawing software packages. Software is not needed to interpret SMILES text strings, and an explanation of how to translate SMILES into structures can be found in Weininger, D., *J. Chem. Inf. Comput. Sci.* 1988, *28*, 31-36. These compounds can also be made using methods well known in the art. It is expected that these compounds when made will have activity similar to those that have been made in the examples above.

c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)nc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3

c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2cn1)nnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)nc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)cc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2cc1)nnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)cc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)nn2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2nn1)nnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)nn2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)cn2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2nc1)nnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)cn2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)noc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)noc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(onc2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)noc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)noc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(onc2c1nnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(onc2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1(onc2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1(onc2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)noc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)coc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)coc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(occ2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)coc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)coc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(occ2c1nnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(occ2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1(occ2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1(occ2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)coc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3

c1(ccc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)nsc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(snc2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(snc2c1nnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(snc2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1(snc2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1(snc2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)csc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)csc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(scc2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)csc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)csc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(scc2c1nnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(scc2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1(scc2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1(scc2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)csc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)n[nH]c2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1([nH]nc2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1([nH]nc2c1nnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1([nH]nc2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1([nH]nc2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1([nH]nc2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)c[nH]c2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1([nH]cc2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1([nH]cc2c1nnc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1([nH]cc2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1([nH]cc2c1nc(N3CCN(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1([nH]cc2c1cnc(N3CCN(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)cccc2N3CCN(Cc4ccc(F)cc4)C=C3)C(=O)C(=O)N(C)C
c1(cccc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cccc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccnc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccnc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccnc2c1cnc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ccnc2c1nc(C(=O)C(=O)N(C)C)cc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ccc2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)cc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)cc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cncc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cncc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ncc2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nncc2c1cc(C(=O)C(=O)N(C)C)cc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CCN(Cc4ccc(F)cc4)C=C3

c1(cc(c(C(=O)C(=O)N(C)C)ncc2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cnnc2c1nc(C(=O)C(=O)N(C)C)cc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ccc2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc2c(cncc2C(=O)C(=O)N(C)C)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(ncnc2c1nc(C(=O)C(=O)N(C)C)cc2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ccn2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cnc2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(C(=O)C(=O)N(C)C)on1)N2CCN(Cc3ccc(F)cc3)C=C2
c1(occ(N2CCN(Cc3ccc(F)cc3)C=C2)c1)C(=O)C(=O)N(C)C
c1([nH]c(C(=O)C(=O)N(C)C)nc1)N2CCN(Cc3ccc(F)cc3)C=C2
c1(cc(C(=O)C(=O)N(C)C)ccc1)N2CCN(Cc3ccc(F)cc3)C=C2
c1(sc(C(=O)C(=O)N(C)C)cn1)N2CCN(Cc3ccc(F)cc3)C=C2
c1(snc(N2CCN(Cc3ccc(F)cc3)C=C2)c1)C(=O)C(=O)N(C)C
c1(sc(N2CCN(Cc3ccc(F)cc3)C=C2)nn1)C(=O)C(=O)N(C)C
c1(nc(N2CCN(Cc3ccc(F)cc3)C=C2)sn1)C(=O)C(=O)N(C)C
c1(cc(C(N2CCN(Cc3ccc(F)cc3)C=C2)C=C4)c4cc1)C(=O)C(=O)N(C)C
c1(cc2c(CC=C2N3CCN(Cc4ccc(F)cc4)C=C3)cc1)C(=O)C(=O)N(C)C
c1(cc(N2CCN(Cc3ccc(F)cc3)C=C2)nnc1)C(=O)C(=O)N(C)C
c1(nc(N2CCN(Cc3ccc(F)cc3)C=C2)cnn1)C(=O)C(=O)N(C)C
c1(ncnc(N2CCN(Cc3ccc(F)cc3)C=C2)n1)C(=O)C(=O)N(C)C
c1(oc(N2CCN(Cc3ccc(F)cc3)C=C2)nn1)C(=O)C(=O)N(C)C
c1(nc(N2CCN(Cc3ccc(F)cc3)C=C2)cnc1)C(=O)C(=O)N(C)C
c1(ccnc(N2CCN(Cc3ccc(F)cc3)C=C2)n1)C(=O)C(=O)N(C)C
c1(nccc(N2CCN(Cc3ccc(F)cc3)C=C2)c1)C(=O)C(=O)N(C)C
c1(scc(N2CCN(Cc3ccc(F)cc3)C=C2)c1)C(=O)C(=O)N(C)C
c1([nH]nc(N2CCN(Cc3ccc(F)cc3)C=C2)c1)C(=O)C(=O)N(C)C
c1(oc(N2CCN(Cc3ccc(F)cc3)C=C2)cn1)C(=O)C(=O)N(C)C
c1(onc(N2CCN(Cc3ccc(F)cc3)C=C2)n1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)no2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)no2)nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc2c(c(C(=O)C(=O)N(C)C)no2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)co2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)co2)nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc2c(c(C(=O)C(=O)N(C)C)co2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)ns2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3

c1(cc2c(c(C(=O)C(=O)N(C)C)ns2)nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc2c(c(C(=O)C(=O)N(C)C)ns2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)cs2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)cs2)nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc2c(c(C(=O)C(=O)N(C)C)cs2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)n[nH]2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(C(C(=O)C(=O)N(C)C)=N[2H]2)nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(C(C(=O)C(=O)N(C)C)=N[2H]2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc2c(C(C(=O)C(=O)N(C)C)=N[2H]2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(C(C(=O)C(=O)N(C)C)=N[2H]2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)c[nH]2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)c[nH]2)nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nc1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc2c(c(C(=O)C(=O)N(C)C)c[nH]2)cn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2oc1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)on1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)on1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(onc2C(=O)C(=O)N(C)C)on1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cnc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nnn2c1oc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n2c(oc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3

c1(n(c2sc1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)sn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)sn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(onc2C(=O)C(=O)N(C)C)sn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cnc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nnn2c1sc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n2c(sc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]c1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)[nH]n1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)[nH]n1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(onc2C(=O)C(=O)N(C)C)[nH]n1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cnc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nnn2c1[nH]c(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n2c([nH]c(N3CCN(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2oc1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)on1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)on1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(snc2C(=O)C(=O)N(C)C)on1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cnc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3

c1(nn(ncc2C(=O)C(=O)N(C)C)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nnn2c1oc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n2c(oc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sc1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)sn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)sn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(snc2C(=O)C(=O)N(C)C)sn1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cnc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nnn2c1sc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n2c(sc(N3CCN(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]c1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)[nH]n1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)[nH]n1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(c2c(snc2C(=O)C(=O)N(C)C)[nH]n1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)nc(C(=O)C(=O)N(C)C)c2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cnc2C(=O)C(=O)N(C)C)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CCN(Cc4ccc(F)cc4)C=C3
c1(nnn2c1[nH]c(N3CCN(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)n2)N3CCN(Cc4ccc(F)cc4)C=C3
c1(n2c([nH]c(N3CCN(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)nc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2cn1)nnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3

c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)nc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)cc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2cc1)nnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)cc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)nn2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2nn1)nnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)nn2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)cn2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2nc1)nnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)cn2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)noc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)noc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(onc2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)noc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)noc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(onc2c1nnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(onc2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1(onc2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1(onc2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)noc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)coc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)coc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(occ2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)coc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)coc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(occ2c1nnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(occ2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1(occ2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1(occ2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)coc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)nsc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(snc2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3

c1(cnc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(snc2c1nnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(snc2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1(snc2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1(snc2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)csc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)csc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(scc2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)csc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)csc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(scc2c1nnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(scc2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1(scc2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1(scc2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)csc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)n[nH]c2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1([nH]nc2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1([nH]nc2c1nnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1([nH]nc2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1([nH]nc2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1([nH]nc2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2n1)c[nH]c2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1([nH]cc2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cnc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1([nH]cc2c1nnc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1([nH]cc2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)nc2)C(=O)C(=O)N(C)C
c1([nH]cc2c1nc(N3CCCC(Cc4ccc(F)cc4)C=C3)cn2)C(=O)C(=O)N(C)C
c1([nH]cc2c1cnc(N3CCCC(Cc4ccc(F)cc4)C=C3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccc(c2c1)cccc2N3CCCC(Cc4ccc(F)cc4)C=C3)C(=O)C(=O)N(C)C
c1(cccc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cccc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccnc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccnc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccnc2c1cnc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ccnc2c1nc(C(=O)C(=O)N(C)C)cc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ccc2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)cc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)cc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cncc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cncc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ncc2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nncc2c1cc(C(=O)C(=O)N(C)C)cc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ncc2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cnnc2c1nc(C(=O)C(=O)N(C)C)cc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ccc2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CCCC(Cc4ccc(F)cc4)C=C3

c1(ncnc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc2c(cncc2C(=O)C(=O)N(C)C)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(ncnc2c1nc(C(=O)C(=O)N(C)C)cc2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ccn2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cnc2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(C(=O)C(=O)N(C)C)on1)N2CCCC(Cc3ccc(F)cc3)C=C2
c1(occ(N2CCCC(Cc3ccc(F)cc3)C=C2)c1)C(=O)C(=O)N(C)C
c1([nH]c(C(=O)C(=O)N(C)C)nc1)N2CCCC(Cc3ccc(F)cc3)C=C2
c1(cc(C(=O)C(=O)N(C)C)ccc1)N2CCCC(Cc3ccc(F)cc3)C=C2
c1(sc(C(=O)C(=O)N(C)C)cn1)N2CCCC(Cc3ccc(F)cc3)C=C2
c1(snc(N2CCCC(Cc3ccc(F)cc3)C=C2)c1)C(=O)C(=O)N(C)C
c1(sc(N2CCCC(Cc3ccc(F)cc3)C=C2)nn1)C(=O)C(=O)N(C)C
c1(nc(N2CCCC(Cc3ccc(F)cc3)C=C2)sn1)C(=O)C(=O)N(C)C
c1(cc(C(N2CCCC(Cc3ccc(F)cc3)C=C2)C=C4)c4cc1)C(=O)C(=O)N(C)C
c1(cc2c(CC=C2N3CCCC(Cc4ccc(F)cc4)C=C3)cc1)C(=O)C(=O)N(C)C
c1(cc(N2CCCC(Cc3ccc(F)cc3)C=C2)nnc1)C(=O)C(=O)N(C)C
c1(nc(N2CCCC(Cc3ccc(F)cc3)C=C2)cnn1)C(=O)C(=O)N(C)C
c1(ncnc(N2CCCC(Cc3ccc(F)cc3)C=C2)n1)C(=O)C(=O)N(C)C
c1(oc(N2CCCC(Cc3ccc(F)cc3)C=C2)nn1)C(=O)C(=O)N(C)C
c1(nc(N2CCCC(Cc3ccc(F)cc3)C=C2)cnc1)C(=O)C(=O)N(C)C
c1(ccnc(N2CCCC(Cc3ccc(F)cc3)C=C2)n1)C(=O)C(=O)N(C)C
c1(nccc(N2CCCC(Cc3ccc(F)cc3)C=C2)c1)C(=O)C(=O)N(C)C
c1(scc(N2CCCC(Cc3ccc(F)cc3)C=C2)c1)C(=O)C(=O)N(C)C
c1([nH]nc(N2CCCC(Cc3ccc(F)cc3)C=C2)c1)C(=O)C(=O)N(C)C
c1(oc(N2CCCC(Cc3ccc(F)cc3)C=C2)cn1)C(=O)C(=O)N(C)C
c1(onc(N2CCCC(Cc3ccc(F)cc3)C=C2)n1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)no2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)no2)nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc2c(c(C(=O)C(=O)N(C)C)no2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)co2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)co2)nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc2c(c(C(=O)C(=O)N(C)C)co2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)ns2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)ns2)nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc2c(c(C(=O)C(=O)N(C)C)ns2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3

c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)cs2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)cs2)nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc2c(c(C(=O)C(=O)N(C)C)cs2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)n[nH]2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(C(C(=O)C(=O)N(C)C)=N[2H]2)nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(C(C(=O)C(=O)N(C)C)=N[2H]2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc2c(C(C(=O)C(=O)N(C)C)=N[2H]2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(C(C(=O)C(=O)N(C)C)=N[2H]2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)c[nH]2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc2c(c(C(=O)C(=O)N(C)C)c[nH]2)nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nc1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc2c(c(C(=O)C(=O)N(C)C)c[nH]2)cn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2oc1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)on1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)on1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(onc2C(=O)C(=O)N(C)C)on1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cnc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nnn2c1oc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n2c(oc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sc1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)sn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)sn1)N3CCCC(Cc4ccc(F)cc4)C=C3

c1(c2c(onc2C(=O)C(=O)N(C)C)sn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cnc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nnn2c1sc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n2c(sc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]c1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)[nH]n1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)[nH]n1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(onc2C(=O)C(=O)N(C)C)[nH]n1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cnc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nnn2c1[nH]c(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n2c([nH]c(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2oc1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)on1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)on1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(snc2C(=O)C(=O)N(C)C)on1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cnc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nnn2c1oc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C

c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n2c(oc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sc1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)sn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)sn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(snc2C(=O)C(=O)N(C)C)sn1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cnc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nnn2c1sc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n2c(sc(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]c1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)[nH]n1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)[nH]n1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(c2c(snc2C(=O)C(=O)N(C)C)[nH]n1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)nc(C(=O)C(=O)N(C)C)c2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cnc2C(=O)C(=O)N(C)C)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(nnn2c1[nH]c(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)C(=O)C(=O)N(C)C
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)n2)N3CCCC(Cc4ccc(F)cc4)C=C3
c1(n2c([nH]c(N3CCCC(Cc4ccc(F)cc4)C=C3)c2)nn1)C(=O)C(=O)N(C)C
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)nc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2cn1)nnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)nc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3

c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)cc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2cc1)nnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)cc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)nn2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2nn1)nnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)nn2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)cn2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2nc1)nnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)cn2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2c1)noc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2n1)noc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(onc2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)noc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cnc(c2c1)noc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(onc2c1nnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(onc2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)nc2)C(=O)C(=O)N(C)C
c1(onc2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)cn2)C(=O)C(=O)N(C)C
c1(onc2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)noc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2c1)coc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2n1)coc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(occ2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)coc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cnc(c2c1)coc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(occ2c1nnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(occ2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)nc2)C(=O)C(=O)N(C)C
c1(occ2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)cn2)C(=O)C(=O)N(C)C
c1(occ2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)coc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2n1)nsc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(snc2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cnc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(snc2c1nnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(snc2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)nc2)C(=O)C(=O)N(C)C
c1(snc2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)cn2)C(=O)C(=O)N(C)C

c1(snc2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)nsc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2c1)csc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2n1)csc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(scc2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)csc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cnc(c2c1)csc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(scc2c1nnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(scc2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)nc2)C(=O)C(=O)N(C)C
c1(scc2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)cn2)C(=O)C(=O)N(C)C
c1(scc2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)csc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2n1)n[nH]c2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1([nH]nc2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cnc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1([nH]nc2c1nnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1([nH]nc2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)nc2)C(=O)C(=O)N(C)C
c1([nH]nc2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)cn2)C(=O)C(=O)N(C)C
c1([nH]nc2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2n1)c[nH]c2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1([nH]cc2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cnc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1([nH]cc2c1nnc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1([nH]cc2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)nc2)C(=O)C(=O)N(C)C
c1([nH]cc2c1nc(N3CC=C(Cc4ccc(F)cc4)CC3)cn2)C(=O)C(=O)N(C)C
c1([nH]cc2c1cnc(N3CC=C(Cc4ccc(F)cc4)CC3)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccc(c2c1)cccc2N3CC=C(Cc4ccc(F)cc4)CC3)C(=O)C(=O)N(C)C
c1(cccc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cccc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccnc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccnc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccnc2c1cnc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ccnc2c1nc(C(=O)C(=O)N(C)C)cc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)ccc2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)cc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)cc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cncc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cncc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)ncc2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nncc2c1cc(C(=O)C(=O)N(C)C)cc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)ncc2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cnnc2c1nc(C(=O)C(=O)N(C)C)cc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)ccc2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)cn2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)nc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc2c(cncc2C(=O)C(=O)N(C)C)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(ncnc2c1nc(C(=O)C(=O)N(C)C)cc2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)ccn2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3

c1(nc(c(C(=O)C(=O)N(C)C)cnc2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(C(=O)C(=O)N(C)C)on1)N2CC=C(Cc3ccc(F)cc3)CC2
c1(occ(N2CC=C(Cc3ccc(F)cc3)CC2)c1)C(=O)C(=O)N(C)C
c1([nH]c(C(=O)C(=O)N(C)C)nc1)N2CC=C(Cc3ccc(F)cc3)CC2
c1(cc(C(=O)C(=O)N(C)C)ccc1)N2CC=C(Cc3ccc(F)cc3)CC2
c1(sc(C(=O)C(=O)N(C)C)cn1)N2CC=C(Cc3ccc(F)cc3)CC2
c1(snc(N2CC=C(Cc3ccc(F)cc3)CC2)c1)C(=O)C(=O)N(C)C
c1(sc(N2CC=C(Cc3ccc(F)cc3)CC2)nn1)C(=O)C(=O)N(C)C
c1(nc(N2CC=C(Cc3ccc(F)cc3)CC2)sn1)C(=O)C(=O)N(C)C
c1(cc(C(N2CC=C(Cc3ccc(F)cc3)CC2)C=C4)c4cc1)C(=O)C(=O)N(C)C
c1(cc2c(CC=C2N3CC=C(Cc4ccc(F)cc4)CC3)cc1)C(=O)C(=O)N(C)C
c1(cc(N2CC=C(Cc3ccc(F)cc3)CC2)nnc1)C(=O)C(=O)N(C)C
c1(nc(N2CC=C(Cc3ccc(F)cc3)CC2)cnn1)C(=O)C(=O)N(C)C
c1(ncnc(N2CC=C(Cc3ccc(F)cc3)CC2)n1)C(=O)C(=O)N(C)C
c1(oc(N2CC=C(Cc3ccc(F)cc3)CC2)nn1)C(=O)C(=O)N(C)C
c1(nc(N2CC=C(Cc3ccc(F)cc3)CC2)cnc1)C(=O)C(=O)N(C)C
c1(ccnc(N2CC=C(Cc3ccc(F)cc3)CC2)n1)C(=O)C(=O)N(C)C
c1(nccc(N2CC=C(Cc3ccc(F)cc3)CC2)c1)C(=O)C(=O)N(C)C
c1(scc(N2CC=C(Cc3ccc(F)cc3)CC2)c1)C(=O)C(=O)N(C)C
c1([nH]nc(N2CC=C(Cc3ccc(F)cc3)CC2)c1)C(=O)C(=O)N(C)C
c1(oc(N2CC=C(Cc3ccc(F)cc3)CC2)cn1)C(=O)C(=O)N(C)C
c1(onc(N2CC=C(Cc3ccc(F)cc3)CC2)n1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)no2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)no2)nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc2c(c(C(=O)C(=O)N(C)C)no2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)co2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)co2)nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc2c(c(C(=O)C(=O)N(C)C)co2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)ns2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)ns2)nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc2c(c(C(=O)C(=O)N(C)C)ns2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)cs2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3

c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)cs2)nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc2c(c(C(=O)C(=O)N(C)C)cs2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)n[nH]2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(C(C(=O)C(=O)N(C)C)=N[2H]2)nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(C(C(=O)C(=O)N(C)C)=N[2H]2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc2c(C(C(=O)C(=O)N(C)C)=N[2H]2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(C(C(=O)C(=O)N(C)C)=N[2H]2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)c[nH]2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc2c(c(C(=O)C(=O)N(C)C)c[nH]2)nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nc1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc2c(c(C(=O)C(=O)N(C)C)c[nH]2)cn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2oc1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)on1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)on1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(onc2C(=O)C(=O)N(C)C)on1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2on1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2on1)cnc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nnn2c1oc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n2c(oc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sc1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)sn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)sn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(onc2C(=O)C(=O)N(C)C)sn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3

c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sn1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sn1)cnc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nnn2c1sc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n2c(sc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]c1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)[nH]n1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)[nH]n1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(onc2C(=O)C(=O)N(C)C)[nH]n1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]n1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]n1)cnc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nnn2c1[nH]c(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n2c([nH]c(N3CC=C(Cc4ccc(F)cc4)CC3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2oc1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)on1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)on1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(snc2C(=O)C(=O)N(C)C)on1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2on1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2on1)cnc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nnn2c1oc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n2c(oc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sc1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3

c1(c2c(sc(C(=O)C(=O)N(C)C)c2)sn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)sn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(snc2C(=O)C(=O)N(C)C)sn1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sn1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sn1)cnc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2s1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nnn2c1sc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n2c(sc(N3CC=C(Cc4ccc(F)cc4)CC3)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]c1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)[nH]n1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)[nH]n1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(c2c(snc2C(=O)C(=O)N(C)C)[nH]n1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]n1)nc(C(=O)C(=O)N(C)C)c2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]n1)cnc2C(=O)C(=O)N(C)C)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(ncc2C(=O)C(=O)N(C)C)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)N3CC=C(Cc4ccc(F)cc4)CC3
c1(nnn2c1[nH]c(N3CC=C(Cc4ccc(F)cc4)CC3)c2)C(=O)C(=O)N(C)C
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)n2)N3CC=C(Cc4ccc(F)cc4)CC3
c1(n2c([nH]c(N3CC=C(Cc4ccc(F)cc4)CC3)c2)nn1)C(=O)C(=O)N(C)C
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)nc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2cn1)nnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)nc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)cc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2cc1)nnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C

c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)cc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cc2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)nn2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2nn1)nnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)nn2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)nn2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nn2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncn(c2c1)c(C(=O)C(=O)N(C)C)cn2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2nc1)nnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncn(c2n1)c(C(=O)C(=O)N(C)C)cn2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2c1)noc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2n1)noc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(onc2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)noc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cnc(c2c1)noc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(onc2c1nnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(onc2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)nc2)C(=O)C(=O)N(C)C
c1(onc2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)cn2)C(=O)C(=O)N(C)C
c1(onc2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)noc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2c1)coc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2n1)coc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(occ2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)coc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cnc(c2c1)coc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(occ2c1nnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(occ2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)nc2)C(=O)C(=O)N(C)C
c1(occ2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)cn2)C(=O)C(=O)N(C)C
c1(occ2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)coc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2c1)nsc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2n1)nsc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(snc2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)nsc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cnc(c2c1)nsc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(snc2c1nnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(snc2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)nc2)C(=O)C(=O)N(C)C
c1(snc2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)cn2)C(=O)C(=O)N(C)C
c1(snc2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)nsc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2c1)csc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2n1)csc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4

c1(scc2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)csc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cnc(c2c1)csc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(scc2c1nnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(scc2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)nc2)C(=O)C(=O)N(C)C
c1(scc2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)cn2)C(=O)C(=O)N(C)C
c1(scc2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)csc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2n1)n[nH]c2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1([nH]nc2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cnc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1([nH]nc2c1nnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1([nH]nc2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)nc2)C(=O)C(=O)N(C)C
c1([nH]nc2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)cn2)C(=O)C(=O)N(C)C
c1([nH]nc2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)n[nH]c2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2n1)c[nH]c2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1([nH]cc2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(ncc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cnc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1([nH]cc2c1nnc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1([nH]cc2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)nc2)C(=O)C(=O)N(C)C
c1([nH]cc2c1nc(C(CC(Cc3ccc(F)cc3)C4)=C4)cn2)C(=O)C(=O)N(C)C
c1([nH]cc2c1cnc(C(CC(Cc3ccc(F)cc3)C4)=C4)n2)C(=O)C(=O)N(C)C
c1(nnc(c2c1)c[nH]c2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccc(c2c1)cccc2C(CC(Cc3ccc(F)cc3)C4)=C4)C(=O)C(=O)N(C)C
c1(cccc2c1cc(C(=O)C(=O)N(C)C)cn2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cccc2c1cc(C(=O)C(=O)N(C)C)nc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccnc2c1cc(C(=O)C(=O)N(C)C)cn2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccnc2c1cc(C(=O)C(=O)N(C)C)nc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccnc2c1cnc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ccnc2c1nc(C(=O)C(=O)N(C)C)cc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)ccc2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)cc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)cc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cncc2c1cc(C(=O)C(=O)N(C)C)cn2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cncc2c1cc(C(=O)C(=O)N(C)C)nc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)ncc2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nncc2c1cc(C(=O)C(=O)N(C)C)cc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)cn2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cnnc2c1cc(C(=O)C(=O)N(C)C)nc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)ncc2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cnnc2c1nc(C(=O)C(=O)N(C)C)cc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)ccc2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)cn2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncnc2c1cc(C(=O)C(=O)N(C)C)nc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc2c(cncc2C(=O)C(=O)N(C)C)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(ncnc2c1nc(C(=O)C(=O)N(C)C)cc2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)ccn2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)cnc2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(C(=O)C(=O)N(C)C)on1)C(CC(Cc2ccc(F)cc2)C3)=C3
c1(occ(C(CC(Cc2ccc(F)cc2)C3)=C3)c1)C(=O)C(=O)N(C)C
c1([nH]c(C(=O)C(=O)N(C)C)nc1)C(CC(Cc2ccc(F)cc2)C3)=C3

c1(cc(C(=O)C(=O)N(C)C)ccc1)C(CC(Cc2ccc(F)cc2)C3)=C3
c1(sc(C(=O)C(=O)N(C)C)cn1)C(CC(Cc2ccc(F)cc2)C3)=C3
c1(snc(C(CC(Cc2ccc(F)cc2)C3)=C3)c1)C(=O)C(=O)N(C)C
c1(sc(C(CC(Cc2ccc(F)cc2)C3)=C3)nn1)C(=O)C(=O)N(C)C
c1(nc(C(CC(Cc2ccc(F)cc2)C3)=C3)sn1)C(=O)C(=O)N(C)C
c1(cc(C(C(CC(Cc2ccc(F)cc2)C3)=C3)C=C4)c4cc1)C(=O)C(=O)N(C)C
c1(cc2c(CC=C2C(CC(Cc3ccc(F)cc3)C4)=C4)cc1)C(=O)C(=O)N(C)C
c1(cc(C(CC(Cc2ccc(F)cc2)C3)=C3)nnc1)C(=O)C(=O)N(C)C
c1(nc(C(CC(Cc2ccc(F)cc2)C3)=C3)cnn1)C(=O)C(=O)N(C)C
c1(ncnc(C(CC(Cc2ccc(F)cc2)C3)=C3)n1)C(=O)C(=O)N(C)C
c1(oc(C(CC(Cc2ccc(F)cc2)C3)=C3)nn1)C(=O)C(=O)N(C)C
c1(nc(C(CC(Cc2ccc(F)cc2)C3)=C3)cnc1)C(=O)C(=O)N(C)C
c1(ccnc(C(CC(Cc2ccc(F)cc2)C3)=C3)n1)C(=O)C(=O)N(C)C
c1(nccc(C(CC(Cc2ccc(F)cc2)C3)=C3)c1)C(=O)C(=O)N(C)C
c1(scc(C(CC(Cc2ccc(F)cc2)C3)=C3)c1)C(=O)C(=O)N(C)C
c1([nH]nc(C(CC(Cc2ccc(F)cc2)C3)=C3)c1)C(=O)C(=O)N(C)C
c1(oc(C(CC(Cc2ccc(F)cc2)C3)=C3)cn1)C(=O)C(=O)N(C)C
c1(onc(C(CC(Cc2ccc(F)cc2)C3)=C3)n1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)no2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)no2)nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)no2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc2c(c(C(=O)C(=O)N(C)C)no2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)no2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)co2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)co2)nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc2c(c(C(=O)C(=O)N(C)C)co2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)ns2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)ns2)nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)ns2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc2c(c(C(=O)C(=O)N(C)C)ns2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)ns2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)cs2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)cs2)nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4

c1(nc2c(c(C(=O)C(=O)N(C)C)cs2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)n[nH]2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)n[nH]2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)n[nH]2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(C(C(=O)C(=O)N(C)C)=N[2H]2)nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(C(C(=O)C(=O)N(C)C)=N[2H]2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc2c(C(C(=O)C(=O)N(C)C)=N[2H]2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(C(C(=O)C(=O)N(C)C)=N[2H]2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)c[nH]2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc2c(c(C(=O)C(=O)N(C)C)c[nH]2)nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nc1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc2c(c(C(=O)C(=O)N(C)C)c[nH]2)cn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)c[nH]2)c2nn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2oc1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)on1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)on1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(onc2C(=O)C(=O)N(C)C)on1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2on1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2on1)cnc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(ncc2C(=O)C(=O)N(C)C)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nnn2c1oc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n2c(oc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sc1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)sn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)sn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(onc2C(=O)C(=O)N(C)C)sn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sn1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4

c1(n(c2sn1)cnc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(ncc2C(=O)C(=O)N(C)C)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nnn2c1sc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n2c(sc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)co2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]c1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(oc(C(=O)C(=O)N(C)C)c2)[nH]n1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)co2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(oc(C(=O)C(=O)N(C)C)n2)[nH]n1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(onc2C(=O)C(=O)N(C)C)[nH]n1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(nc(C(=O)C(=O)N(C)C)o2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]n1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]n1)cnc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(ncc2C(=O)C(=O)N(C)C)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nnn2c1[nH]c(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n2c([nH]c(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2oc1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)on1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)on1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(snc2C(=O)C(=O)N(C)C)on1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2on1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2on1)cnc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2on1)cc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(ncc2C(=O)C(=O)N(C)C)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nnn2c1oc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(n(c2oc1)nc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n2c(oc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sc1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)sn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)sn1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(snc2C(=O)C(=O)N(C)C)sn1)C(CC(Cc3ccc(F)cc3)C4)=C4

c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2o1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sn1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sn1)cnc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2sn1)cc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(ncc2C(=O)C(=O)N(C)C)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2s1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nnn2c1sc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(n(c2sc1)nc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n2c(sc(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)nn1)C(=O)C(=O)N(C)C
c1(cc(c(C(=O)C(=O)N(C)C)cs2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]c1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(sc(C(=O)C(=O)N(C)C)c2)[nH]n1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(c(C(=O)C(=O)N(C)C)cs2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(sc(C(=O)C(=O)N(C)C)n2)[nH]n1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(c2c(snc2C(=O)C(=O)N(C)C)[nH]n1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nc(nc(C(=O)C(=O)N(C)C)s2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cc2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(cn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]n1)nc(C(=O)C(=O)N(C)C)c2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]n1)cnc2C(=O)C(=O)N(C)C)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n(c2[nH]n1)cc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(ncc2C(=O)C(=O)N(C)C)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)nc2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nn(c(C(=O)C(=O)N(C)C)cn2)c2[nH]1)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(nnn2c1[nH]c(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)C(=O)C(=O)N(C)C
c1(n(c2[nH]c1)nc(C(=O)C(=O)N(C)C)n2)C(CC(Cc3ccc(F)cc3)C4)=C4
c1(n2c([nH]c(C(CC(Cc3ccc(F)cc3)C4)=C4)c2)nn1)C(=O)C(=O)N(C)C

Biological Activity Assay

The activity of the compounds in examples 1-6 as p38 inhibitors has been shown by the following assays. The other compounds listed above, which have not yet been made, are predicted to have activity in these assays as well.

p38α Biochemical Assay

The p38α assay employed is based on measurement of total ATP turnover following enzyme incubation with substrate in the presence of ATP with the use of a luminescent detection reagent (Cambrex PKlight). The assays were performed in 1536-well white opaque plates. The final volume was 7.5005 μL as prepared prepared from the addition of 5 ul of kinase reaction (p38 alpah+MapkapK2+ATP) with 0.0005 μL compound dissolved in DMSO, and 2.5 μl of the detection

reagent. Assay buffer contains the following reagents to give final concentration in the assay: 200mM Tris, 100mM $MgCl_2$, 1.5mM EGTA, 4mM $CaCl_2$, 20mM MOPS, 1mM EDTA, 1% glycerol, 0.1% B-Mecaptoethanol, and 1mg/ml BSA. Test compounds are pinned using proprietary pintool technology (Kalypsys, Inc) and delivered as 40nl amounts into the 5ul mixture of active p38 alpha enzyme (Upstate Biotechnology) and MapkapK2 (Upstate Biotechnology) whole protein as a substrate for phosphorylation in the presence of 1.4 uM final concentration ATP. Reactions are incubated at 30C for 2 hours and detection reagent is added in 2.5ul/well amounts. Assay is read using a Perkin Elmer Viewlux. Data is represented as IC50 in uM as determined by GraphPad Prism (GraphPad Software, Inc).

TNF-α Production by LPS-Stimulated Mice

Male Lewis rats (180-200 g) were injected intraperitoneally with lipopolysaccharide (LPS) (50 μg/kg of E. coli strain 0111:B4, Sigma) suspended in sterile saline. Ninety minutes later, mice were sedated by CO_2:O_2 inhalation and a blood sample was obtained. Serum was separated and analyzed for TNF-α concentrations by commercial ELISA assay per the manufacturer's instructions (RAT TNFα kit Cat # DY510E R&D Systems). Test compounds were administered orally at various times before LPS injection. The compounds were dosed either as suspensions or as solutions in various vehicles or solubilizing agents.

Compounds were dosed 1 hour before LPS stimulation. Rats were anaesthetized with Isofluor and injected i.v. with 0.3 mg/kg of LPS* in a volume of 0.3 ml sterile saline. Ninety minutes after the LPS injection, blood samples were collected into heparin tubes for preparation of plasma samples. Repression of TNFα production is assessed by commercial ELISA from R&D Systems and report below in Table 3.

TNF-α ELISA Cellular Assay

Maintenance and Differentiation of the U937 Human Histiocytic Lymphoma Cell Line:

U937 cells (ATCC) were propagated in RPMI 1640 containing 10% fetal bovine serum, 100 IU/ml penicillin, 100 μg/ml streptomycin, and 2 mM glutamine (Gibco). Fifty million cells in 100 ml media were induced to terminal monocytic differentiation by 24 hour incubation with 20 ng/ml phorbol 12-myristate 13-acetate (Sigma). The cells were washed by centrifugation (200×g for 5 min) and resuspended in 100 ml fresh medium. After 24-48 hours, the cells were harvested, centrifuged, and resuspended in culture medium at 0.5 million cells/ml for LPS stimulation.

LPS Stimulation of TNF Production by U937 Cells:

U937 cells (0.005 ml, 0.5 million/ml) were incubated with compound (0.001-10 μM, final concentration) for 1 hour 1536 well TC treated plates. Compounds were prepared as 10 mM stock solutions in DMSO and diluted in culture medium to yield a final DMSO concentration of <1% in the cell assay. LPS (E coli, 100 ng/ml final concentration) was then added at a volume of 2ul. After 4 hour incubation at 37°

C., the amount of TNF-α released in the culture medium was quantitated by ELISA (Human TNFα kit Cat # DY210E, R&D Systems). Inhibitory potency is expressed as IC50 (μM).

Results

IC_{50} data were obtained for the compounds provided herein. Data for selected compounds is shown in the Table below. "NT" indicates that the compound was not tested in a particular assay.

Table 1

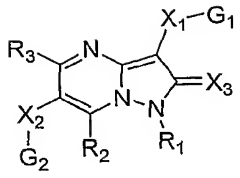
Example Number	P38 Assay IC_{50} + signifies ≤ 1μM − signifies >1μM	TNF-α ELISA Cellular Assay IC_{50} + signifies ≤ 1μM − signifies >1μM	LPS-Stimulated TNFα Percent Inhibition at 10 mg/kg + signifies ≥ 10%
1	+	+	NT
2	+	+	NT
3	+	NT	NT
4	+	NT	+
5	+	NT	NT
6	+	NT	NT

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS

What is claimed is:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

X_1 and X_2 are independently selected from the group consisting of a bond, –O–, –NR_4–, alkenyl, alkynyl, –C(O)–, sulfanyl, sulfinyl, –SO_2–, –$SO_2N(R_4)$–, –$N(R_4)S(O)_2$–, –$C(R_5)_2$–, –$C(R_5)_2N(R_4)$–, $N(R_4)C(O)$–, –$C(O)N(R_4)$–, –$N(R_4)C(O)N(R_4)$–, and –OC(O)O–, wherein each group is drawn with its left end attached to G_1 or G_2 and its right end attached to the core structure;

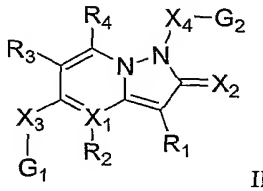
G_1 and G_2 are independently selected from the group consisting of aryl, cycloalkyl, heteroaryl, and heterocyclo, any of which may be optionally substituted;

X_3 is selected from the group consisting of oxygen or sulfur;

R_1, R_4, and R_5 are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylamino, alkylene, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkenyl, arylalkyl, arylalkynyl, arylcarbonyl, arylsulfonyl, cyanoalkenyl, cycloalkyl, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonyl, heterocycle, heterocycloalkenyl, heterocycloalkyl, and hydroxyalkyl; and

R^2 and R^3 are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, cyano, cyanoalkenyl, cycloalkyl, halo, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocycloalkenyl, heterocycloalkyl, hydroxy, hydroxyalkyl, and nitro.

2. A compound of Formula II:



II

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

X^1 is selected from the group consisting of carbon or nitrogen;

X^2 is selected from the group consisting of oxygen or sulfur;

X^3 is selected from the group consisting of a bond, –O–, $–NR^5–$, alkylene, alkenylene, alkynylene, –C(O)–, –S–, –S(O)–, $–SO_2–$, $–SO_2N(R^5)–$, $–N(R^5)SO_2–$, $–C(R^6)_2N(R^5)–$, $–N(R^5)C(O)–$, $–C(O)N(R^5)–$, $–N(R^5)C(O)N(R^5)–$, and –OC(O)O–;

X^4 is selected from the group consisting of a bond, alkyl, –C(O)–, $–SO_2–$, $–N(R^5)SO_2–$, and $–N(R^5)C(O)–$;

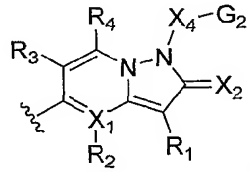
G^1 and G^2 are independently selected from the group consisting of aryl, cycloalkyl, heteroaryl, and heterocyclo, any of which may be optionally substituted;

R^1 and R^6 are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylamino, alkylene, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkenyl, arylalkyl, arylalkynyl, arylcarbonyl, arylsulfonyl, cyanoalkenyl, cycloalkyl, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonyl, heterocycle, heterocycloalkenyl, heterocycloalkyl, and hydroxyalkyl;

R^2, R^3, and R^4 are independently absent or selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, cyano, cyanoalkenyl, cycloalkyl, halo, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocycloalkenyl, heterocycloalkyl, hydroxy, hydroxyalkyl, and nitro; and

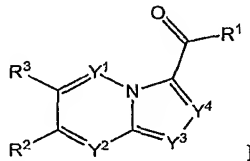
R^5 is selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylamino, alkylene, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkenyl, arylalkyl, arylalkynyl, arylcarbonyl, arylsulfonyl, cyanoalkenyl, cycloalkyl, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonyl, heterocycle, heterocycloalkenyl, heterocycloalkyl, hydroxyalkyl, any of which may be optionally substituted and Z, wherein

Z has the structural formula III:



III

3. A compound of Formula IV:



IV

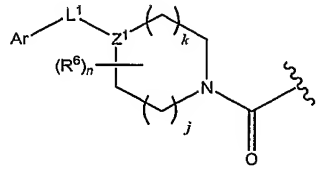
or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

Y^1, Y^2, Y^3 and Y^4 are each independently selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of acyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylcarbonyl, alkylthio, alkylthiocarbonyl, amino, aminoalkyl, amido, aryl, arylalkoxy, arylalkyl, arylalkylamino, arylalkylthio, arylamino, arylamido, aryloxy, arylthio, carboxy, cycloalkyl, cycloalkylcarbonyl, haloalkoxy, haloalkoxycarbonyl, haloalkyl, heteroaryl, heteroarylcarbonyl, heteroarylamino, heteroarylamido, heteroaryloxy, heteroarylthio, heterocyclo, heterocyclocarbonyl, hydroxy, and thiol;

R^2 is selected from the group consisting of hydrogen, acyl, alkoxy, alkoxyalkyl, alkyl, alkylamino, amino, amido, alkylamino, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and sulfonate;

R^3 is of the Formula V:



V;

Z^1 is selected from the group consisting of N and CR^4;

j, *k*, and *n* are independently selected to be from zero to four;

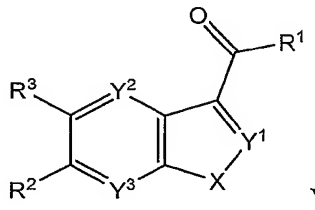
L^1 is selected from the group consisting of a bond, alkyl, –C(O)–, $–NR^5–$, –O–, –S–, –S(O)–, $–SO_2–$, –C(O)O–, –OC(O)–, $–N(R^5)C(O)–$, $–C(O)N(R^5)–$, $–N(R^5)C(O)O–$, $–N(R^5)C(O)N(R^5)–$, $–OC(O)N(R^5)–$, $–N(R^5)C(O)S–$, and $–OC(O)N(R^5)–$;

Ar is selected from the group consisting of aryl and heteroaryl;

each R^4 is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkyl, alkylamino, amido, amino, aminoalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and hydroxyalkyl; and

each R^5, and R^6 are independently selected from the group consisting of hydrogen, alkoxy, alkyl, halo, haloalkyl, hydroxy, and hydroxyalkyl.

4. A compound of Formula VI



VI

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

X is selected from the group consisting of –O–, $–NR^5–$, and –S—;

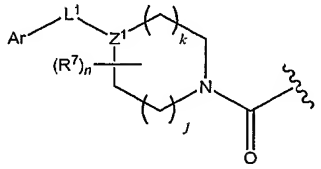
Y^1, Y^2, and Y^3 are each independently selected from the group consisting of CR^6 and N;

R^1 is selected from the group consisting of acyl, alkoxy, alkoxycarbonyl, alkyl,

alkylamino, alkylcarbonyl, alkylthio, alkylthiocarbonyl, amino, aminoalkyl, amido, aryl, arylalkoxy, arylalkyl, arylalkylamino, arylalkylthio, arylamino, arylamido, aryloxy, arylthio, carboxy, cycloalkyl, cycloalkylcarbonyl, haloalkoxy, haloalkoxycarbonyl, haloalkyl, heteroaryl, heteroarylcarbonyl, heteroarylamino, heteroarylamido, heteroaryloxy, heteroarylthio, heterocyclo, heterocyclocarbonyl, hydroxy, and thiol;

R^2 is selected from the group consisting of hydrogen, acyl, alkoxy, alkoxyalkyl, alkyl, alkylamino, amino, amido, alkylamino, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and sulfonate;

R^3 is of Formula VII



VII;

Z^1 is selected from the group consisting of N and CR^4;

j, *k*, and *n* are independently selected to be from zero to four;

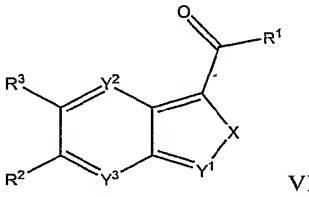
L^1 is selected from the group consisting of a bond, alkyl, –C(O)–, $–NR^5–$, –O–, –S–, –S(O)–, $–SO_2–$, –C(O)O–, –OC(O)–, $–N(R^5)C(O)–$, $–C(O)N(R^5)–$, $–N(R^5)C(O)O–$, $–N(R^5)C(O)N(R^5)–$, $–OC(O)N(R^5)–$, $–N(R^5)C(O)S–$, and $–OC(O)N(R^5)–$;

Ar is selected from the group consisting of aryl and heteroaryl;

each R^4 is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkyl, alkylamino, amido, amino, aminoalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and hydroxyalkyl; and

each R^5, R^6, and R^7 are independently selected from the group consisting of hydrogen, alkoxy, alkyl, halo, haloalkyl, hydroxy, and hydroxyalkyl.

5. A compound of Formula VIII:



VIII

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

X is selected from the group consisting of –O–, $–NR^5–$, and –S—;

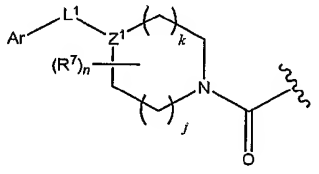
Y^1, Y^2, and Y^3 are each independently selected from the group consisting of CR^6 and N;

R^1 is selected from the group consisting of acyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylcarbonyl, alkylthio, alkylthiocarbonyl, amino, aminoalkyl, amido, aryl, arylalkoxy, arylalkyl, arylalkylamino, arylalkylthio, arylamino, arylamido, aryloxy,

arylthio, carboxy, cycloalkyl, cycloalkylcarbonyl, haloalkoxy, haloalkoxycarbonyl, haloalkyl, heteroaryl, heteroarylcarbonyl, heteroarylamino, heteroarylamido, heteroaryloxy, heteroarylthio, heterocyclo, heterocyclocarbonyl, hydroxy, and thiol;

R^2 is selected from the group consisting of hydrogen, acyl, alkoxy, alkoxyalkyl, alkyl, alkylamino, amino, amido, alkylamino, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and sulfonate;

R^3 is of the Formula IX



IX;

Z^1 is selected from the group consisting of N and CR^4;

j, *k*, and *n* are independently selected to be from zero to four;

L^1 is selected from the group consisting of a bond, alkyl, $-C(O)-$, $-NR^5-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-C(O)O-$, $-OC(O)-$, $-N(R^5)C(O)-$, $-C(O)N(R^5)-$, $-N(R^5)C(O)O-$, $-N(R^5)C(O)N(R^5)-$, $-OC(O)N(R^5)-$, $-N(R^5)C(O)S-$, and $-OC(O)N(R^5)-$;

Ar is selected from the group consisting of aryl and heteroaryl;

each R^4 is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkyl, alkylamino, amido, amino, aminoalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and hydroxyalkyl; and

each R^5, R^6, and R^7 are independently selected from the group consisting of hydrogen, alkoxy, alkyl, halo, haloalkyl, hydroxy, and hydroxyalkyl.

6. The compound or composition as recited in any one of Claims 1-5 for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the inhibition of p38.
7. The compound as recited in Claim 6, selected from the group consisting of Examples 1-6.
8. A pharmaceutical composition comprising a compound as recited in any one of Claims 1-5 together with a pharmaceutically acceptable carrier.
9. A method of inhibition of p38 comprising contacting p38 with a compound as recited in any one of Claims 1-5.
10. A method of treatment of a p38-mediated disease comprising the administration of a therapeutically effective amount of a compound as recited in any one of Claims 1-5 to a patient in need thereof.
11. A method of treatment of a p38-mediated disease in a patient in need thereof comprising the administration of
    a. a therapeutically effective amount of a compound as recited in any one of Claims 1-5; and

b. another therapeutic agent.

12. The method as recited in Claim 10 and Claim 11 wherein said disease is inflammatory disorders.
13. The method as recited in Claim 12 wherein said inflammatory disorder is selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease, inflammatory pain and psoriasis.
14. A method for achieving an effect in a patient comprising the administration of a therapeutically effective amount of a compound as recited in Claim 1-5 to a patient, wherein the effect is selected from the group consisting of inhibition of p38, treatment of a p38-mediated disease, and treatment of an inflammatory disorder.